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(54) **USE OF INHIBITORS OF THE ACTIVITY OR FUNCTION OF PI3K**

VERWENDUNG VON INHIBITOREN DER AKTIVITÄT ODER FUNKTION VON PI3K

UTILISATION D'INHIBITEURS DE L'ACTIVITÉ OU DE LA FONCTION DE PI3K

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Description

FIELD OF THE INVENTION

[0001] The invention relates to the subject matter defined in the claims.

BACKGROUND OF THE INVENTION

[0002] Parasitic infections still represent one of the most important causes of morbidity and mortality worldwide. Among the parasites that cause human and animal pathology the phylum apicomplexa comprises a group of vector-borne parasites that is responsible for a wide variety of serious illnesses including but not limited to malaria, leishmaniasis and trypanosomiasis. Malaria alone infects 5-10% of humanity and causes around two million deaths per year. [Schofield et al, "Immunological processes in malaria pathogenesis", Nat Rev Imm 2005], [Schofield L, "Intravascular infiltrates and organ-specific inflammation in malaria pathogenesis"], [Mishra et al, "TLRs in CNS Parasitic infections", Curr Top Micro Imm 2009], [Bottieu et al, "Therapy of vector-borne protozoan infections in nonendemic settings", Expert Rev. Anti infect. Ther., 2011].

[0003] Toll-like receptors (TLRs) are germ-line encoded, phylogenetically ancient molecules that recognize evolutionary conserved structural relevant molecules (known as pathogen - associated molecular patterns (PAMPs)) within microbial pathogens. Various different cell types including cells of the immune system express TLRs and are thereby able to detect the presence of PAMPs. So far 10 functional TLR family members (TLR1-10) have been described in humans, all of which recognize specific PAMP molecules. Following recognition of these specific PAMPs TLRs induce and orchestrate the immuneresponse of the host to infections with bacteria, viruses, fungi and parasites. [Hedayat et al, "Targeting of TLRs: a decade of progress in combating infectious disease", review, Lancet Infectious disease 2011], [Kwai et al, "TLRs and their crosstalk with other innate receptors in infection and immunity", review, Immunity May-2011].

[0004] The immune system of the infected host responds to infection with the TLR induced production of pro-inflammatory cytokines mainly of the T-helper 1 type (Th1). While adequate amounts of these cytokines are beneficial and required to clear the infection an overproduction of these mediators is harmful to the host and associated with immune mediated pathology including neuropathology and tissue damage with severe and often fatal consequences. One prominent and highly relevant example of such immune mediated pathology is acute and cerebral malaria (CM) which causes severe clinical symptoms and is often fatal. [Schofield et al, "Immunological processes in malaria pathogenesis", Nat Rev Imm 2005], [Schofield L, "Intravascular infiltrates and organ-specific inflammation in malaria pathogenesis"], [Mishra et al, "TLRs in CNS Parasitic infections", Curr Top Micro Imm 2009], [Bottieu et al, "Therapy of vector-borne protozoan infections in nonendemic settings", Expert Rev. Anti infect. Ther., 2011] [Hedayat et al, "Targeting of TLRs: a decade of progress in combating infectious disease", review, Lancet Infectious disease 2011]. Despite progress made in treatment and eradication of malaria, the mortality rate that is associated with severe malaria, including CM remains unacceptably high. Strategies directed solely at the eradication of the parasite in the host might therefore not be sufficient to prevent neurological complications and death in all cases of CM. Development of new innovative adjunct therapeutic strategies to efficiently reduce the CM-associated mortality and morbidity that is caused, in part, by host-mediated immunopathology remains therefore an urgent medical need [Higgins et al, "Immunopathogenesis of falciparum malaria: implications for adjunctive therapy in the management of severe and cerebral malaria", Expert Rev. Anti Infect. Ther. 2011].

[0005] Recently further evidence has been provided that TLR9 plays a key role in the recognition and response to parasites including but not limited to Plasmodium, Leishmania, Trypanosoma and Toxoplasma [Gowda et al, "The Nucleosome is the TLR9-specific Immunostimulatory component of plasmodium falciparum that activates DCs", PLoS ONE, June 2011], [Peixoto-Rangel et al, "Candidate gene analysis of ocular toxoplasmosis in Brazil: evidence for a role for TLR9", Mem Inst Oswaldo Cruz 2009], [Pellegrini et al, "The role of TLRs and adoptive immunity in the development of protective or pathological immune response triggered by the Trypanosoma cruzi protozoan", Future Microbiol 2011] and that interference with the activation of TLRs including TLR9 represents a promising strategy to prevent the deleterious inflammatory responses in severe and cerebral malaria [Franklin et al, "Therapeutical targeting of nucleic acid-sensing TLRs prevents experimental cerebral malaria", PNAS 2011].

[0006] Malaria is an infectious disease caused by four protozoan parasites: Plasmodium falciparum; Plasmodium vivax; Plasmodium ovale; and Plasmodium malaria. These four parasites are typically transmitted by the bite of an infected female Anopheles mosquito. Malaria is a problem in many parts of the world and over the last few decades the malaria burden has steadily increased. An estimated 1-3 million people die every year from malaria - mostly children under the age of 5. This increase in malaria mortality is due in part to the fact that Plasmodium falciparum, the deadliest malaria parasite, has acquired resistance against nearly all available antimalarial drugs, with the exception of the artemisinin derivatives.

[0007] Leishmaniasis is caused by one or more than 20 varieties of parasitic protozoa that belong to the genus Leishmania, and is transmitted by the bite of female sand flies. Leishmaniasis is endemic in about 88 countries, including

many tropical and sub-tropical areas. There are four main forms of Leishmaniasis. Visceral leishmaniasis, also called kala-azar, is the most serious form and is caused by the parasite *Leishmania donovani*. Patients who develop visceral leishmaniasis can die within months unless they receive treatment. The two main therapies for visceral leishmaniasis are the antimony derivatives sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantim®). Sodium stibogluconate has been used for about 70 years and resistance to this drug is a growing problem. In addition, the treatment is relatively long and painful, and can cause undesirable side effects.

[0008] Human African Trypanosomiasis, also known as sleeping sickness, is a vector-borne parasitic disease. The parasites concerned are protozoa belonging to the *Trypanosoma* Genus. They are transmitted to humans by tsetse fly (*Glossina* Genus) bites which have acquired their infection from human beings or from animals harboring the human pathogenic parasites.

[0009] Chagas disease (also called American Trypanosomiasis) is another human parasitic disease that is endemic amongst poor populations on the American continent. The disease is caused by the protozoan parasite *Trypanosoma cruzi*, which is transmitted to humans by blood-sucking insects. The human disease occurs in two stages: the acute stage, which occurs shortly after infection and the chronic stage, which can develop over many years. Chronic infections result in various neurological disorders, including dementia, damage to the heart muscle and sometimes dilation of the digestive tract, as well as weight loss. Untreated, the chronic disease is often fatal. The drugs currently available for treating Chagas disease are Nifurtimox and benznidazole. However, problems with these current therapies include their diverse side effects, the length of treatment, and the requirement for medical supervision during treatment. Furthermore, treatment is really only effective when given during the acute stage of the disease. Resistance to the two frontline drugs has already occurred. The antifungal agent Amphotericin b has been proposed as a second-line drug, but this drug is costly and relatively toxic.

[0010] Toxoplasmosis is endemic through most of the world, which can infect a large proportion of the adult population. However, its prevalence differs in different countries. It is estimated to infect at least 10% of adults in northern temperate countries and more than half of adults in Mediterranean and tropical countries. *Toxoplasma gondii* is a ubiquitous, obligate intracellular protozoan and is considered to be the most common cause of infective retinitis in humans, which depends on a variety of factors, including climate, hygiene, and dietary habits. The course of disease in immunocompetent adults is usually asymptomatic and self-limiting. As soon as infection has occurred, the parasite forms latent cysts in the retina and in other organs of the body, which can reactivate years after the initial infection giving rise to acute retinochoroiditis and the formation of new retinochoroidal lesions. [Arevalo et al, "Ocular Toxoplasmosis in the developing world", Internat. Ophthalm. Clin 2010]

[0011] Neurocysticercosis is the most common parasitic disease of the CNS (incidence ~2.5 million worldwide) caused by the larvae of *Taenia solium*. The disease has a long asymptomatic phase in humans characterized by the absence of a detectable inflammatory response surrounding the parasite. The overall immune response during the asymptomatic phase is of the Th2 phenotype. However, the destruction of larvae by therapeutic treatment or by normal parasite attrition causes a strong inflammatory response, often consisting of a chronic granulomatous reaction and manifestation of typical symptoms of the disease. The immune response in the CNS of symptomatic patients consists of an overt Th1 phenotype or a mixed Th1, Th2, and Th3 response, depending upon the absence or presence of granulomas. The hyperinflammatory response prevailing during the symptomatic phase in the CNS is responsible for the severe neuropathology and mortality associated with neurocysticercosis [Mishra et al, "TLRs in CNS Parasitic infections", Curr Top Micro Imm 2009].

[0012] In view of the foregoing there is a strong need for the development of novel effective treatment options for the management of parasitic diseases including the diseases mentioned above, addressing especially the associated immunopathology.

SUMMARY OF THE INVENTION

[0013] It has been found that PI3K inhibitors, wherein said inhibitors have an inhibitory action on the PI3K isoform delta, and/or pharmaceutically acceptable salts and/or solvates thereof exhibit anti-inflammatory properties including functional inhibition of TLR9 and are suitable for the treatment of diseases or disorders that are caused by or related to TLR9 mediated immunopathology or TLR9 mediated disbalance of pro- and anti-inflammatory responses.

[0014] The disclosure therefore provides a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and/or pharmaceutically acceptable salts and/or solvates thereof for use in the treatment of a condition, a disease or disorder caused by a parasite selected from a parasite of the *Plasmodium* genus, for example *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* or *Plasmodium malariae*; a parasite of the *Trypanosoma* genus, for example *Trypanosoma cruzi*; a parasite of the *Leishmania* genus, for example *Leishmania donovani*; a parasite of the *Toxoplasma* genus, for example *Toxoplasma gondii* or a Helminth, for example *Taenia solium*, via functional inhibition of TLR9 of the infected subject.

[0015] The invention provides a PI3K inhibitor as defined in the claims, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and/or pharmaceutically acceptable salts and/or solvates thereof for use in the treatment of

immunopathology in a subject suffering from a disease or disorder selected from acute and cerebral, via functional inhibition of TLR9 of the infected subject.

[0016] The invention further provides a pharmaceutical composition comprising a PI3K inhibitor, as defined in the claims, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and/or pharmaceutically acceptable salts and/or solvates thereof for use in the treatment of immunopathology in a subject suffering from a disease or disorder selected from acute and cerebral malaria, via functional inhibition of TLR9 of the infected subject.

DESCRIPTION OF THE DRAWINGS

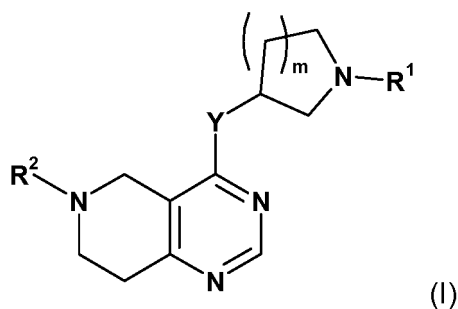
[0017]

Figure 1 discloses the X-ray Powder Diffraction Pattern of Example 1 citrate salt
Figure 2 discloses the X-ray Powder Diffraction Pattern of Example 1 fumarate salt
Figure 3 discloses the X-ray Powder Diffraction Pattern of Example 1 napadisylate salt
Figure 4 discloses the X-ray Powder Diffraction Pattern of Example 67 phosphate salt
Figure 5 discloses the X-ray Powder Diffraction Pattern of Example 67 HCl salt
Figure 6 discloses the X-ray Powder Diffraction Pattern of Example 67 hippurate salt
Figure 7 discloses the X-ray Powder Diffraction Pattern of Example 1 anhydrous form
Figure 8 discloses the X-ray Powder Diffraction Pattern of Example 1 trihydrate
Figure 9 discloses the X-ray Powder Diffraction Pattern of Example 67 anhydrous form

DETAILED DESCRIPTION OF THE INVENTION

[0018] As defined in the claims, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is disclosed in WO2012/004299 (PCT/EP2011/061393).

[0019] As defined in the claims, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a tetrahydro-pyrido-pyrimidine compound of the formula (I) and/or pharmaceutically acceptable salts and/or solvates thereof,



wherein

Y is selected from O or NR³;

R¹ is selected from phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, or

-C(O)-R⁴

wherein

R⁴ is selected from C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, C₁-C₈-alkoxy-C₁-C₈-alkyl, C₁-C₈-alkyl-sulfonyl-C₁-C₈-alkyl, heterocyclyl, heterocyclyl-oxy, heterocyclyl-C₁-C₈-alkyl, C₃-C₁₂-cycloalkyl, C₃-C₁₂-cycloalkyl-C₁-C₈-alkyl, heteroaryl, heteroaryl-oxy, heteroaryl-C₁-C₈-alkyl, hydroxy, C₁-C₈-alkoxy, amino, N-C₁-C₈-alkylamino or N,N-di-C₁-C₈-alkyl-amino,

wherein 'C₁-C₈-alkyl' in N-C₁-C₈-alkyl-amino and N,N-di-C₁-C₈-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C₁-C₄-alkoxy;

wherein 'C₃-C₁₂-cycloalkyl' in C₃-C₁₂-cycloalkyl and C₃-C₁₂-cycloalkyl-C₁-C₈-alkyl may be unsubstituted or substituted by 1-5 substituents independently selected from oxo, halogen, C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hy-

droxy-C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkoxy-C₁-C₈-alkyl, amino, N-C₁-C₈-alkyl-amino, N,N-di-C₁-C₈-alkyl-amino, C₁-C₈-alkyl-carbonyl, halo-C₁-C₈-alkyl-carbonyl, hydroxy-C₁-C₈-alkyl-carbonyl or C₁-C₈-alkoxy-C₁-C₈-alkyl-carbonyl;

wherein 'heterocyclyl' is selected from oxiranyl, aziridinyl, oxetanyl, thiethanyl, acetitanyl, pyrrolidinyl, tetrahydrofuranlyl, tetrahydrothiophenyl, 2,3-dihydrofuranlyl, 2,5-dihydrofuranlyl, 2,3-dihydrothiophenyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, piperazinyl, azepanyl, thiepanyl or oxepanyl; each of which is unsubstituted or substituted by 1-5 substituents independently selected from oxo, halogen, C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkoxy-C₁-C₈-alkyl, amino, N-C₁-C₈-alkyl-amino, N,N-di-C₁-C₈-alkyl-amino, C₁-C₈-alkyl-carbonyl, halo-C₁-C₈-alkyl-carbonyl, hydroxy-C₁-C₈-alkyl-carbonyl or C₁-C₈-alkoxy-C₁-C₈-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

wherein 'heteroaryl' is selected from

furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl or 1,3,5-triazinyl; each of which is unsubstituted or substituted by 1-5 substituents independently selected from halogen, C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkoxy-C₁-C₈-alkyl, amino, N-C₁-C₈-alkyl-amino, N,N-di-C₁-C₈-alkyl-amino, C₁-C₈-alkyl-carbonyl, halo-C₁-C₈-alkyl-carbonyl, hydroxy-C₁-C₈-alkyl-carbonyl or C₁-C₈-alkoxy-C₁-C₈-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

R² is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl or isoquinolinyl, each of which is unsubstituted or substituted by 1-5 substituents independently selected from halogen, cyano, nitro, C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkoxy-C₁-C₈-alkyl, amino, N-C₁-C₈-alkyl-amino, N,N-di-C₁-C₈-alkyl-amino, C₁-C₈-alkyl-carbonyl, halo-C₁-C₈-alkyl-carbonyl, hydroxy-C₁-C₈-alkyl-carbonyl or C₁-C₈-alkoxy-C₁-C₈-alkyl-carbonyl;

R³ is selected from H, C₁-C₄-alkyl or halo-C₁-C₄-alkyl; and

m is selected from 0 or 1.

[0020] Unless specified otherwise, the term "compounds of formula (I)" refers to compounds of formula (I), subformulae thereof, salts of the compound, hydrates or solvates of the compounds, as well as all stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds (including deuterium substitutions).

[0021] As used herein, the term "a", "an", "the" and similar terms used in the context of the present invention, especially in the context of the claims, are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

[0022] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language, *e.g.* "such as", provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

[0023] The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense. Where compounds of formula (I) are mentioned, this is meant to include also the tautomers and N-oxides of the compounds of formula (I).

Tautomers, such as tautomers between keto- and enol form, lactam- and lactim form, amid form and imidic acid form or enamine form and imine form, can be present for example in the R₁ or R₂ portion of compounds of formula (I). The nitrogen atoms of the tetrahydro-pyrido-pyrimidine core of the compounds of formula (I) as well as nitrogen containing heterocyclyl and heteroaryl residues can form N-oxides.

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

[0024] The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

As used herein, the term "alkyl" refers to a fully saturated branched, including single or multiple branching, or unbranched hydrocarbon moiety having up to 20 carbon atoms. Unless otherwise provided, alkyl refers to hydrocarbon moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, sec-

butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like. Typically, alkyl groups have 1-7, more preferably 1-4 carbons.

[0025] As used herein, the term "halo-alkyl" refers to an alkyl as defined herein, which is substituted by one or more halo groups as defined herein. The halo-alkyl can be mono-halo-alkyl, di-halo-alkyl or poly-halo-alkyl including per-halo-alkyl. A mono-halo-alkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Di-halo-alkyl and poly-halo-alkyl groups can have two or more of the same halo atoms or a combination of different halo groups within the alkyl. Typically the poly-halo-alkyl contains up to 12, or 10, or 8, or 6, or 4, or 3, or 2 halo groups. Non-limiting examples of halo-alkyl include fluoro-methyl, di-fluoro-methyl, tri-fluoro-methyl, chloro-methyl, di-chloro-methyl, tri-chloro-methyl, penta-fluoro-ethyl, hepta-fluoro-propyl, di-fluoro-chloro-methyl, di-chloro-fluoro-methyl, di-fluoro-ethyl, di-fluoro-propyl, di-chloro-ethyl and dichloro-propyl. A per-halo-alkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms.

[0026] As used herein, for compounds of formula (I), the term "heterocyclyl" or "heterocyclic" refers to a 3 to 7 membered monocyclic or 7 to 10 membered saturated or partially saturated ring or ring system, which contains at least one heteroatom selected from N, O and S, where the N and S can also optionally be oxidized to various oxidation states. 'Heterocyclyl' can be attached at a heteroatom or a carbon atom. 'Heterocyclyl' can include fused or bridged rings as well as spirocyclic rings. Examples of heterocycles include oxiranyl, aziridinyl, oxetanyl, thiethanyl, acetitanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, 2,3-dihydrothiophenyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, piperazinyl, azepanyl, thiepanyl and oxepanyl.

[0027] As used herein, for compounds of formula (I), the term "heteroaryl" refers to a 4-, 5-, 6-, or 7-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic unsaturated ring or ring system - carrying the highest possible number of conjugated double bonds in the ring(s), which contains at least one heteroatom selected from N, O and S, wherein the N and S can also optionally be oxidized to various oxidation states. 'Heteroaryl' can be attached at a heteroatom or a carbon atom. 'Heteroaryl' can include fused or bridged rings as well as spirocyclic rings. Examples of heteroaryl include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl and 1,3,5-triazinyl.

[0028] As used herein, the term "cycloalkyl" refers to saturated or partially unsaturated monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms. Unless otherwise provided, cycloalkyl refers to cyclic hydrocarbon groups having between 3 and 10 ring carbon atoms or between 3 and 7 ring carbon atoms. Exemplary bicyclic hydrocarbon groups include octahydroindyl, decahydronaphthyl. Exemplary tricyclic hydrocarbon bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl. Exemplary tetracyclic hydrocarbon groups include adamantyl.

[0029] As used herein, the term "oxy" refers to an -O- linking group.

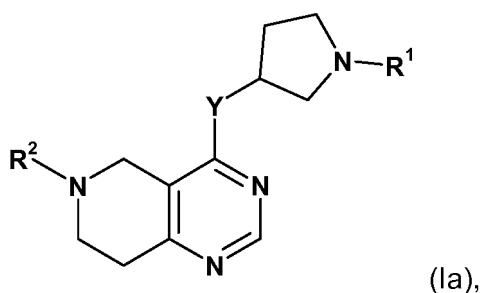
[0030] As used herein, the term "carboxy" or "carboxyl" is -COOH.

[0031] As used herein, all substituents are written in a way to show the order of functional groups (groups) they are composed of. The functional groups are defined herein above.

[0032] "Treatment" includes prophylactic (preventive) and therapeutic treatment as well as the delay of progression of a disease or disorder.

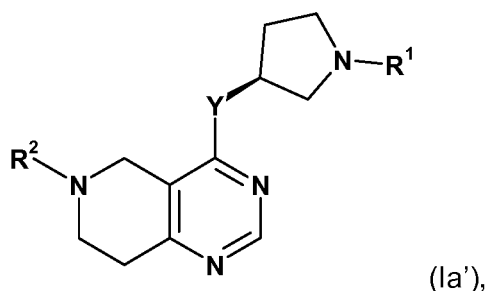
[0033] Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

[0034] In one embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ia)



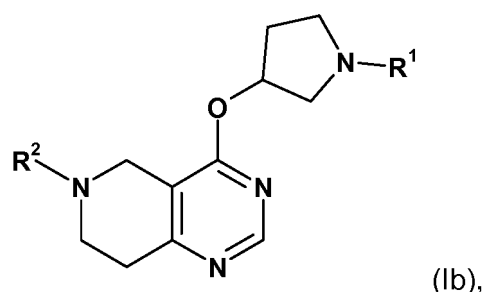
wherein R¹, R² and Y are as defined above.

[0035] In one embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ia')



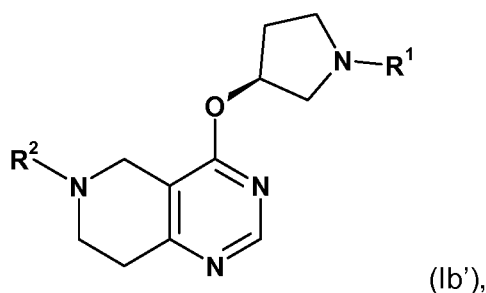
wherein R¹, R² and Y are as defined above.

[0036] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ib)



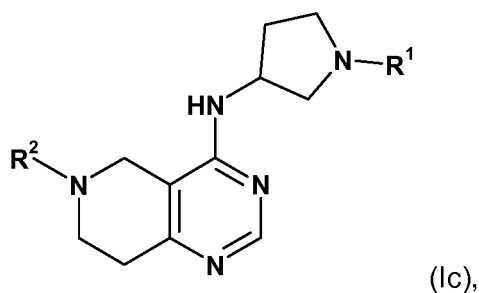
wherein R¹ and R² are as defined above.

[0037] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ib')



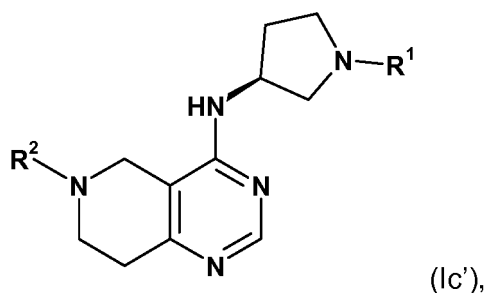
wherein R¹ and R² are as defined above.

[0038] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ic)



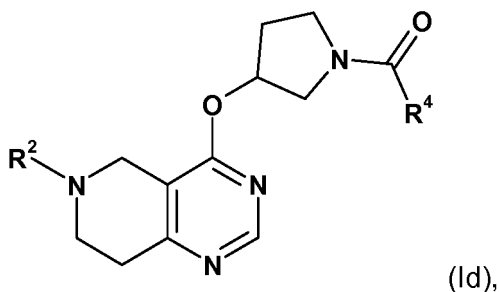
wherein R¹ and R² are as defined above.

[0039] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ic')



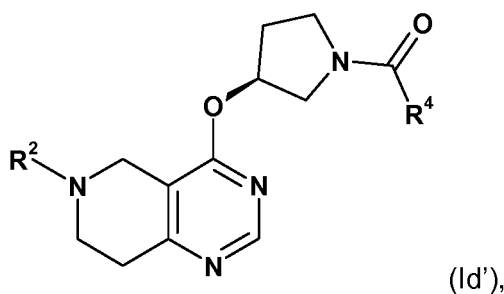
wherein R¹ and R² are as defined above.

[0040] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Id)



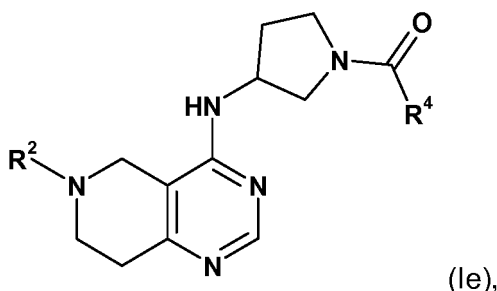
wherein R⁴ and R² are as defined above.

[0041] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Id')



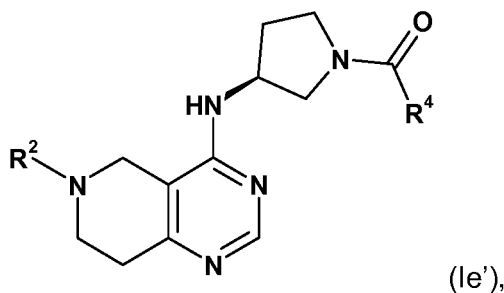
wherein R^4 and R^2 are as defined above.

[0042] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ie)



wherein R^4 and R^2 are as defined above.

[0043] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ie')



wherein R^4 and R^2 are as defined above.

[0044] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R^2 is selected from naphthyl, pyridyl or pyrimidinyl; each of which is unsubstituted or substituted by 1-3 substituents independently selected from halogen, cyano, nitro, C_1 - C_8 -alkyl, halo- C_1 - C_8 -alkyl, hydroxy- C_1 - C_8 -alkyl, hydroxyl, C_1 - C_8 -alkoxy, C_1 - C_8 -alkoxy- C_1 - C_8 -alkyl, amino, N- C_1 - C_8 -alkyl-amino, N,N-di- C_1 - C_8 -alkyl-amino, C_1 - C_8 -alkyl-carbonyl, halo- C_1 - C_8 -alkyl-carbonyl, hydroxy- C_1 - C_8 -alkyl-carbonyl or C_1 - C_8 -alkoxy- C_1 - C_8 -alkyl-carbonyl.

[0045] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R^2 is selected from 3-pyridyl or 5-pyrimidinyl; each of which is substituted by 1-2 substituents independently selected from halogen, cyano, nitro, C_1 - C_8 -alkyl, halo- C_1 - C_8 -alkyl, hydroxy- C_1 - C_8 -alkyl, hydroxyl, C_1 - C_8 -alkoxy, C_1 - C_8 -alkoxy- C_1 - C_8 -alkyl, amino, N- C_1 - C_8 -alkyl-amino, N,N-di- C_1 - C_8 -alkyl-amino, C_1 - C_8 -alkyl-carbonyl, halo- C_1 - C_8 -alkyl-carbonyl, hydroxy- C_1 - C_8 -alkyl-carbonyl or C_1 - C_8 -alkoxy- C_1 - C_8 -alkyl-carbonyl, wherein one substituent is located in the para position relative to the point of connection of R^2 to the core of the compound.

[0046] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R^2 is selected from 3-pyridyl or 5-pyrimidinyl; each of which is substituted by 1-2 substituents independently selected from halogen, cyano, C_1 - C_4 -alkyl, halo- C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy or amino, wherein one substituent is located in the para position relative to the point of connection of R^2 to the core of the compound.

[0047] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R^2 is selected from 3-pyridyl or 5-pyrimidinyl; each of which is substituted by 1-2 substituents independently selected from fluoro, chloro, cyano, methyl, trifluoromethyl,

methoxy or amino, wherein one substituent is located in the para position relative to the point of connection of R² to the core of the compound.

[0048] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia) or (Ia') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R³ is H.

[0049] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R¹ is selected from phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl or 1,3,5-triazinyl.

[0050] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R¹ is selected from pyridyl or pyrimidinyl.

[0051] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R¹ is -C(O)-R⁴, wherein R⁴ is as defined above.

[0052] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R¹ is -C(O)-R⁴, wherein R⁴ is as defined above.

[0053] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') wherein R¹ is -C(O)-R⁴; or a compound of the formulae (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein

R⁴ is selected from C₁-C₈-alkyl, C₁-C₈-alkoxy-C₁-C₈-alkyl, heterocyclyl, heterocyclyl-C₁-C₈-alkyl, C₃-C₁₂-cycloalkyl, heteroaryl, C₁-C₈-alkoxy or N,N-di-C₁-C₈-alkyl-amino, wherein 'C₁-C₈-alkyl' in N,N-di-C₁-C₈-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C₁-C₄-alkoxy;

wherein 'C₃-C₁₂-cycloalkyl' in C₃-C₁₂-cycloalkyl may be unsubstituted or substituted by 1-3 substituents independently selected from oxo, halogen, C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkyl-carbonyl;

wherein 'heterocyclyl' is selected from pyrrolidinyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl or piperazinyl; each of which is unsubstituted or substituted by 1-3 substituents independently selected from oxo, halogen, C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkyl-carbonyl;

wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

wherein 'heteroaryl' is selected from

furanyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, 1,3,4-oxadiazolyl, pyridyl, pyrazinyl; each of which is unsubstituted or substituted by 1-3 substituents independently selected from halogen, C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkylcarbonyl;

wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states.

[0054] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') wherein R¹ is -C(O)-R⁴; or a compound of the formulae (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein

R⁴ is selected from heterocyclyl, C₄-C₈-cycloalkyl or heteroaryl;

wherein 'C₃-C₁₂-cycloalkyl' may be unsubstituted or substituted by 1-3 substituents independently selected from fluoro, C₁-C₄-alkyl, hydroxyl, C₁-C₄-alkoxy;

wherein 'heterocyclyl' is selected from pyrrolidinyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl or piperazinyl; each of which is unsubstituted or substituted by 1-3 substituents independently selected from oxo,

halogen, C₁-C₄-alkyl, hydroxyl, C₁-C₄-alkyl-carbonyl;
 wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms
 can also optionally be oxidized to various oxidation states;
 wherein 'heteroaryl' is selected from
 5 furanyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, 1,3,4-oxadiazolyl, pyridyl, pyrazinyl; each of which is
 unsubstituted or substituted by 1-3 substituents independently selected from C₁-C₄-alkyl, hydroxyl;
 wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can
 also optionally be oxidized to various oxidation states.

10 **[0055]** In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory
 action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') wherein R¹ -C(O)-R⁴;
 or a compound of the formulae (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof,
 wherein

15 R⁴ is selected from heterocyclyl;
 wherein 'heterocyclyl' is selected from pyrrolidinyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl
 or piperazinyl; each of which is unsubstituted or substituted by 1-3 substituents independently selected from oxo,
 halogen, C₁-C₄-alkyl, hydroxyl, C₁-C₄-alkyl-carbonyl;
 wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms
 20 can also optionally be oxidized to various oxidation states.

[0056] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory
 action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') wherein R¹ is -C(O)-R⁴;
 or a compound of the formulae (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof,
 25 wherein

R⁴ is selected from C₁-C₈-alkyl, C₁-C₈-alkoxy-C₁-C₈-alkyl, C₁-C₈-alkoxy or N,N-di-C₁-C₈-alkyl-amino,
 wherein 'C₁-C₈-alkyl' in N,N-di-C₁-C₈-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or
 C₁-C₄-alkoxy.
 30

[0057] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory
 action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') wherein R¹ is -C(O)-R⁴;
 or a compound of the formulae (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof,
 wherein
 35

R⁴ is selected from C₁-C₈-alkyl.

[0058] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory
 action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') wherein R¹ is -C(O)-R⁴;
 40 or a compound of the formulae (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof,
 wherein

R² is selected from 3-pyridyl or 5-pyrimidinyl; each of which is substituted by 1-2 substituents independently selected
 from fluoro, chloro, cyano, methyl, trifluoromethyl, methoxy or amino, wherein one substituents is located in the para
 45 position relative to the point of connection of R² to the core of the compound and R⁴ is selected from heterocyclyl;
 wherein 'heterocyclyl' is selected from pyrrolidinyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl
 or piperazinyl; each of which is unsubstituted or substituted by 1-3 substituents independently selected from oxo,
 halogen, C₁-C₄-alkyl, hydroxyl, C₁-C₄-alkyl-carbonyl;
 wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms
 50 can also optionally be oxidized to various oxidation states.

[0059] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory
 action on the PI3K isoform delta, is a compound of the formulae (I), (Ia), (Ia'), (Ib), (Ib'), (Ic) or (Ic') wherein R¹ is -C(O)-R⁴;
 or a compound of the formulae (Id), (Id'), (Ie) or (Ie') and/or a pharmaceutically acceptable salt and/or a solvate thereof,
 55 wherein

R² is selected from 3-pyridyl or 5-pyrimidinyl; each of which is substituted by 1-2 substituents independently selected
 from fluoro, chloro, cyano, methyl, trifluoromethyl, methoxy or amino, wherein one substituents is located in the para

position relative to the point of connection of R² to the core of the compound and R⁴ is selected from C₁-C₈-alkyl, C₁-C₈-alkoxy-C₁-C₈-alkyl, C₁-C₈-alkoxy or N,N-di-C₁-C₈-alkyl-amino, wherein 'C₁-C₈-alkyl' in N,N-di-C₁-C₈-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C₁-C₄-alkoxy.

5

[0060] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a relevant compound listed in the Examples section below.

[0061] In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, is a compound of the formula (I), selected from

- 10 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 {(S)-3-[6-(2,4-Dimethoxy-pyrimidin-5-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 15 {3-[6-(2,4-Dimethoxy-pyrimidin-5-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 2-Methoxy-5-{4-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 20 2-Methoxy-5-{4-[1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 1-{(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-propan-1-one;
 1-{3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-propan-1-one;
 25 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 2-Amino-5-{4-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 30 2-Amino-5-{4-[1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 (S)-(3-(6-(5-Fluoro-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 35 (3-(6-(5-Fluoro-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (S)-2-Methoxy-5-(4-(1-(2-methoxyacetyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;
 2-Methoxy-5-(4-(1-(2-methoxyacetyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;
 (S)-5-(4-(1-(Cyclopentanecarbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-methoxynicotinonitrile;
 40 5-(4-(1-(Cyclopentanecarbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-methoxynicotinonitrile;
 (2,4-Dimethyl-oxazol-5-yl)-{(S)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 (2,4-Dimethyl-oxazol-5-yl)-{3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 45 Furan-3-yl-{(S)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 Furan-3-yl-{3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 50 Furan-3-yl-{(S)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 Furan-3-yl-{3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-3H-imidazol-4-yl)-methanone;
 55 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-3H-imidazol-4-yl)-methanone;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2-me-

- thyl-oxazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2-methyl-oxazol-4-yl)-methanone;
 (3-Methoxy-cyclobutyl)-{(S)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 (3-Methoxy-cyclobutyl)-{3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 ({(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-4-yl)-methanone;
 ({3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-4-yl)-methanone;
 1-(4-{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-piperidin-1-yl)-ethanone;
 1-(4-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-piperidin-1-yl)-ethanone;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(4-methyl-oxazol-5-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(4-methyl-oxazol-5-yl)-methanone;
 5-{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-1H-pyridin-2-one;
 5-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-1H-pyridin-2-one;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone;
 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-4-yl-methanone;
 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-4-yl-methanone;
 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-5-yl-methanone;
 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-5-yl-methanone;
 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2-methyl-oxazol-4-yl)-methanone;
 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2-methyl-oxazol-4-yl)-methanone;
 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2,2-dimethyl-tetrahydro-pyran-4-yl)-methanone;
 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2,2-dimethyl-tetrahydro-pyran-4-yl)-methanone;
 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2,4-dimethyl-oxazol-5-yl)-methanone;
 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2,4-dimethyl-oxazol-5-yl)-methanone;
 (4,4-Difluoro-cyclohexyl)-{(S)-3-[6-(5,6-dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 (4,4-Difluoro-cyclohexyl)-f3-[6-(5,6-dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 2-Methoxy-5-{4-[(S)-1-(2-tetrahydro-pyran-4-yl-acetyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 2-Methoxy-5-{4-[1-(2-tetrahydro-pyran-4-yl-acetyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 5-{4-[(S)-1-(2,4-Dimethyl-oxazole-5-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxy-nicotinonitrile;
 5-{4-[1-(2,4-Dimethyl-oxazole-5-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxy-

nicotinonitrile;

5-{4-[(S)-1-(2,2-Dimethyl-tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxy-nicotinonitrile;

5-{4-[1-(2,2-Dimethyl-tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxy-nicotinonitrile;

{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(5-methyl-oxazol-4-yl)-methanone;

{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(5-methyl-oxazol-4-yl)-methanone;

{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone;

{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone;

{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-isoxazol-4-yl)-methanone;

{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-isoxazol-4-yl)-methanone;

{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-isoxazol-4-yl)-methanone;

{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-isoxazol-4-yl)-methanone;

Isoxazol-3-yl-{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

Isoxazol-3-yl-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

Isoxazol-5-yl-{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

Isoxazol-5-yl-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

2-Methoxy-5-{4-[(S)-1-(thiazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

2-Methoxy-5-{4-[1-(thiazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

2-Methoxy-5-{4-[(S)-1-(1-methyl-1H-pyrazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

2-Methoxy-5-{4-[1-(1-methyl-1H-pyrazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

2-Methoxy-5-{4-[(S)-1-(1-methyl-1H-pyrazole-3-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

2-Methoxy-5-{4-[1-(1-methyl-1H-pyrazole-3-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

(2,2-Dimethyl-tetrahydro-pyran-4-yl)-{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

(2,2-Dimethyl-tetrahydro-pyran-4-yl)-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

(1,1-Dioxo-hexahydro-1 λ 6*-thiopyran-4-yl)-{(S)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

(1,1-Dioxo-hexahydro-1 λ 6*-thiopyran-4-yl)-{3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

(S)-(2,4-Dimethyloxazol-5-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;

(2,4-Dimethyloxazol-5-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;

(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(thiazol-5-yl)methanone;

(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(thiazol-5-yl)methanone;

(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-methyl-1H-pyrazol-5-yl)methanone;

- (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-methyl-1H-pyrazol-5-yl)methanone;
- 4-((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)pyrrolidin-2-one;
- 5 4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)pyrrolidin-2-one;
- (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyridin-3-yl)methanone;
- (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyridin-3-yl)methanone;
- 10 (S)-(1H-Imidazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
- (1H-Imidazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
- 15 5-((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)pyrrolidin-2-one;
- 5-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)pyrrolidin-2-one;
- (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyridin-4-yl)methanone;
- 20 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyridin-4-yl)methanone;
- (S)-(1,3-Dimethyl-1H-pyrazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
- 25 (1,3-Dimethyl-1H-pyrazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
- (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1H-pyrazol-4-yl)methanone;
- (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1H-pyrazol-4-yl)methanone;
- 30 (S)-(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(5-methyl-1,3,4-oxadiazol-2-yl)methanone;
- (3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(5-methyl-1,3,4-oxadiazol-2-yl)methanone;
- 35 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyrazin-2-yl)methanone;
- (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyrazin-2-yl)methanone;
- (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-methyl-1H-imidazol-4-yl)methanone;
- 40 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-methyl-1H-imidazol-4-yl)methanone;
- {{(S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(1-methyl-1H-pyrazol-4-yl)-methanone;
- 45 {3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(1-methyl-1H-pyrazol-4-yl)-methanone;
- {{(S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-thiazol-4-yl-methanone;
- {3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-thiazol-4-yl-methanone;
- 50 {{(S)-3-[6-(5-Chloro-6-methoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone;
- {3-[6-(5-Chloro-6-methoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone;
- 55 (S)-(3-(6-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
- (3-(6-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;

- (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)azetidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
- {(S)-3-[6-(2-Methoxy-pyrimidin-5-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
- 5 {3-[6-(2-Methoxy-pyrimidin-5-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
- [(S)-3-(6-Quinolin-3-yl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl]-(tetrahydro-pyran-4-yl)-methanone;
- [3-(6-Quinolin-3-yl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl]-(tetrahydro-pyran-4-yl)-methanone;
- 10 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
- (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
- 15 (S)-1-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-3,3-dimethylbutan-1-one;
- 1-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-3,3-dimethylbutan-1-one;
- 1-((S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-propan-1-one;
- 20 1-{3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-propan-1-one;
- 2-Methoxy-5-[4-((S)-1-propionyl-pyrrolidin-3-yloxy)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-nicotinonitrile;
- 2-Methoxy-5-[4-(1-propionyl-pyrrolidin-3-yloxy)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-nicotinonitrile;
- 25 (S)-6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-4-(1-(pyridin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;
- 6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-4-(1-(pyridin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;
- (S)-6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-4-(1-(pyrimidin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;
- 30 6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-4-(1-(pyrimidin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;
- (S)-1-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)propan-1-one;
- 35 1-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)propan-1-one;
- (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
- (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
- 40 (S)-2-Methoxy-5-(4-(1-(tetrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-ylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;
- 2-Methoxy-5-(4-(1-(tetrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-ylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;
- 45 (S)-1-(4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidine-1-carbonyl)piperidin-1-yl)ethanone;
- 1-(4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidine-1-carbonyl)piperidin-1-yl)ethanone;
- (2,2-Dimethyltetrahydro-2H-pyran-4-yl)((S)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
- 50 (2,2-Dimethyltetrahydro-2H-pyran-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
- (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)methanone;
- 55 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)methanone;
- ((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)((1s,4R)-4-methoxycyclohexyl)methanone;

- (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)((1s,4R)-4-methoxycyclohexyl)methanone;
 ((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)((1r,4S)-4-methoxycyclohexyl)methanone;
 5 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)((1r,4S)-4-methoxycyclohexyl)methanone;
 ((1s,4R)-4-Hydroxycyclohexyl)((S)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 ((1s,4R)-4-Hydroxycyclohexyl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 10 ((1r,4S)-4-Hydroxycyclohexyl)((S)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 ((1r,4S)-4-Hydroxycyclohexyl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 15 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(1-methyl-1H-imidazol-4-yl)methanone;
 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(1-methyl-1H-imidazol-4-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)methanone;
 20 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-4-yl)methanone;
 25 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-4-yl)methanone;
 (2,2-Dimethyltetrahydro-2H-pyran-4-yl)((S)-3-(6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 (2,2-Dimethyltetrahydro-2H-pyran-4-yl)(3-(6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 30 (S)-1-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)propan-1-one;
 1-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)propan-1-one;
 35 (S)-(3-(6-(5-Chloro-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (3-(6-(5-Chloro-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 40 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (Tetrahydro-pyran-4-yl)-((S)-3-(6-(5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)-methanone;
 45 (Tetrahydro-pyran-4-yl)-{3-(6-(5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl}-methanone;
 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(4-methylpiperazin-1-yl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(4-methylpiperazin-1-yl)methanone;
 50 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(morpholino)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(morpholino)methanone;
 55 (S)-(4-Hydroxypiperidin-1-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
 4-Hydroxypiperidin-1-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;

(S)-N-(2-Hydroxyethyl)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)-N-methylpyrrolidine-1-carboxamide;

N-(2-Hydroxyethyl)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)-N-methylpyrrolidine-1-carboxamide;

(S)-1-(4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)piperazin-1-yl)ethanone;

1-(4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)piperazin-1-yl)ethanone;

(S)-2-Methoxy-5-(4-(1-(morpholine-4-carbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;

2-Methoxy-5-(4-(1-(morpholine-4-carbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;

(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(oxazol-4-yl)methanone;

(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(oxazol-4-yl)methanone;

1-(4-((S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl)-piperidin-1-yl)-ethanone;

1-(4-{3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-piperidin-1-yl)-ethanone;

((S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(3-methyl-3H-imidazol-4-yl)-methanone;

{3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(3-methyl-3H-imidazol-4-yl)-methanone;

((S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-oxazol-5-yl-methanone;

{3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-oxazol-5-yl-methanone;

((S)-3-[6-(6-Methoxy-pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone; or

{3-[6-(6-Methoxy-pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone.

[0062] In view of the close relationship between the compounds of the formula (I) in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the compounds or a compound of the formula (I) hereinbefore and hereinafter is to be understood as referring to the compound in free form and/or also to one or more salts thereof, as appropriate and expedient, as well as to one or more solvates, e.g. hydrates.

[0063] The compounds of formula (I) or salts thereof are prepared in accordance with processes known *per se*, though not previously described for the manufacture of the compounds of the formula (I).

[0064] As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the PI3K inhibitors, wherein said inhibitors have an inhibitory action on the PI3K isoform delta, and, which typically are not biologically or otherwise undesirable. In many cases, the PI3K inhibitors, wherein said inhibitors have an inhibitory action on the PI3K isoform delta, used in the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlorotheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns 1 to

12 of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed.

[0065] As used herein, the term "subject" refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

[0066] As used herein, the term "inhibit", "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

[0067] As used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat", "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treat", "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treat", "treating" or "treatment" refers to preventing or delaying the progression of the disease or disorder.

[0068] As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

[0069] The term "administration" or "administering" of the subject compound means providing a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, to a subject in need of treatment. Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order, and in any route of administration.

[0070] The invention also provides a pharmaceutical composition comprising a PI3K inhibitor as defined in the claims, wherein said inhibitors have an inhibitory action on the PI3K isoform delta. The invention thus provides

- a pharmaceutical composition comprising a PI3K inhibitor as defined in the claims, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and one or more carriers / excipients;

- a pharmaceutical composition comprising a therapeutically effective amount of a PI3K inhibitor as defined in the claims, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and one or more pharmaceutically acceptable carriers / excipients.

[0071] As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289-1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

[0072] The present invention provides the use of a pharmaceutical composition comprising a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and a pharmaceutically acceptable carrier. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present invention can

be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers and buffers, etc.

[0073] Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with

- a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
- b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also
- c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired
- d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or
- e) absorbents, colorants, flavors and sweeteners.

[0074] Tablets may be either film coated or enteric coated according to methods known in the art.

[0075] Suitable compositions for oral administration include an effective amount of a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed.

[0076] Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[0077] Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

[0078] Suitable compositions for transdermal application include an effective amount of a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the subject. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, optionally with carriers, optionally a rate controlling barrier to deliver the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, of the skin of the subject at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[0079] Suitable compositions for topical application, e.g., to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, e.g., for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, e.g., for the treatment of skin cancer, e.g., for prophylactic use in sun creams, lotions, sprays and the like. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0080] As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder, either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids, from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

[0081] The present invention further provides the use of anhydrous pharmaceutical compositions and dosage forms comprising the PI3K inhibitors, wherein said inhibitors have an inhibitory action on the PI3K isoform delta, as active ingredients, since water may facilitate the degradation of certain compounds.

[0082] Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers, e. g., vials, blister packs, and strip packs.

[0083] The invention further provides the use of pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

[0084] Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONICS®.

[0085] Suitable excipients / carriers may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc. Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

[0086] The dosage of the active ingredient depends upon the disease to be treated and upon the species, its age, weight, and individual condition, the individual pharmacokinetic data, and the mode of administration. The amount of active ingredient in a formulation can vary within the full range employed by those skilled in the art.

[0087] Pharmaceutical compositions comprising a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta in association with at least one pharmaceutical acceptable carrier (such as excipient and/or diluent) may be manufactured in conventional manner, e.g. by means of conventional mixing, granulating, coating, dissolving or lyophilising processes.

[0088] The invention also relates to a combination comprising a PI3K inhibitor as defined in the claims, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and one or more additional active ingredients. The invention thus provides

- a combination in particular a pharmaceutical combination, comprising a therapeutically effective amount of a PI3K inhibitor as defined in the claims, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and one or more therapeutically active agents, for the treatment of acute and cerebral malaria.

- a combined pharmaceutical composition, adapted for simultaneous or sequential administration, comprising a therapeutically effective amount of a PI3K inhibitor as defined in the claims, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, as defined herein; therapeutically effective amount(s) of one or more combination partners for the treatment of acute and cerebral malaria.

[0089] The term "a therapeutically effective amount" of a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, refers to an amount of the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc.

[0090] "Combination" refers to either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and a combination partner (e.g. an other drug as explained below, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g. synergistic effect. The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected combination

partner to a single subject in need thereof, e.g. a patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[0091] The PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. immunosuppressive or immunomodulating agents or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, or a chemotherapeutic agent, e.g. a malignant cell anti-proliferative agent. For example, PI3K inhibitors, wherein said inhibitors have an inhibitory action on the PI3K isoform delta, may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a mTOR inhibitor, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, ABT578, AP23573, TAFA-93, biolimus-7 or biolimus-9; an ascomycin having immuno-suppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; leflunomide; mizoribine; mycophenolic acid or salt; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; a PKC inhibitor, e.g. as disclosed in WO 02/38561 or WO 03/82859, e.g. the compound of Example 56 or 70; a JAK3 kinase inhibitor, e.g. N-benzyl-3,4-dihydroxybenzylidene-cyanoacetamide α -cyano-(3,4-dihydroxy)-N-benzylcinnamamide (Tyrphostin AG 490), prodigiosin 25-C (PNU156804), [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P131), [4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P154), [4-(3',5'-dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline] WHI-P97, KRX-211, 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxopropionitrile, in free form or in a pharmaceutically acceptable salt form, e.g. mono-citrate (also called CP-690,550), or a compound as disclosed in WO 04/052359 or WO 05/066156; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40, CD45, CD52, CD58, CD80, CD86 or their ligands; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or-3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or antihistamines; or antitussives, or a bronchodilatory agent; or an angiotensin receptor blockers; or an anti-infectious agent.

[0092] PI3K inhibitors, wherein said inhibitors has an inhibitory action on the PI3K isoform delta, may also be used to advantage in combination with each other or in combination with other therapeutic agents, especially other anti-malarial agents. Such anti-malarial agents include, but are not limited to proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, inhaled NO, L-arginine, Dipropyleneetri-amine NONOate (NO donor), Rosiglitzone (PPAR γ agonist), activated charcoal, Erythropoietin, Levamisole, and pyronaridine.

[0093] PI3K inhibitors, wherein said inhibitors have an inhibitory action on the PI3K isoform delta, may also be used to advantage in combination with each other or in combination with other therapeutic agents, such as used for the treatment of Leishmaniasis, Trypanosomiasis, Toxoplasmosis and Neurocysticercosis. Such agents include, but are not limited to chloroquine sulfate, atovaquone-proguanil, artemether-lumefantrine, quinine-sulfate, artesunate, quinine, doxycycline, clindamycin, meglumine antimoniate, sodium stibogluconate, miltefosine, ketoconazole, pentamidine, amphotericin B (AmB), liposomal-AmB, paromomycine, eflornithine, nifurtimox, suramin, melarsoprol, prednisolone, benznidazole, sulfadiazine, pyrimethamine, clindamycin, trimetopim, sulfamethoxazole, azitromycin, atovaquone, dexamethasone, praziquantel, albendazole, beta-lactams, fluoroquinolones, macrolides, aminoglycosides, sulfadiazine and pyrimethamine.

[0094] The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International, e.g., IMS World Publications.

The above-mentioned compounds, which can be used in combination with s, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, can be prepared and administered as described in the art, such as in the documents cited above.

PI3K inhibitors, wherein said inhibitors have an inhibitory action on the PI3K isoform delta, may also be used to advantage

in combination with known therapeutic processes.

Experimental details:

[0095] Insofar as the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as described hereafter.

[0096] The following examples are illustrative of the invention without any limitation.

[0097] Abbreviations, LCMS Methods used, Purification methods, X-ray Powder Diffraction-instrumentation, Preparation of intermediate compounds, Preparation of examples including synthesis schemes are described on pages 62-64, 64-66, 66, 66, 66-84 and 85-166 of WO2012/004299 respectively.

[0098] The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-2000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

[0099] The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The PI3K inhibitor, as defined in the claims, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, can be applied *in vitro* in the form of solutions, e.g., aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

Biological evaluation

[0100] The activity of a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, can be assessed by the following *in vitro* & *in vivo* methods.

Biological assays

1 Determination of enzymatic PI3K alpha and PI3K delta isoform inhibition

1.1 Test of lipid kinase activity

[0101] The efficacy of the PI3K inhibitors, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, can be demonstrated as follows:

The kinase reaction is performed in a final volume of 50 μ l per well of a half area COSTAR, 96 well plate. The final concentrations of ATP and phosphatidyl inositol in the assay are 5 μ M and 6 μ g/mL, respectively. The reaction is started by the addition of PI3 kinase, e.g. PI3 kinase δ .

[0102] p110 δ . The components of the assay are added per well as follows:

- 10 μ l test compound in 5% DMSO per well in columns 2-1.
- Total activity is determined by addition 10 μ l of 5% vol/vol DMSO in the first 4 wells of column 1 and the last 4 wells of column 12.
- The background is determined by addition of 10 μ M control compound to the last 4 wells of column 1 and the first 4 wells of column 12.
- 2 mL 'Assay mix' are prepared per plate:

1.912 mL of HEPES assay buffer

8.33 μ l of 3 mM stock of ATP giving a final concentration of 5 μ M per well

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1 μ l of [^{33} P]ATP on the activity date giving 0.05 μ Ci per well

30 μ l of 1 mg/mL PI stock giving a final concentration of 6 μ g/mL per well

5 5 μ l of 1 M stock $MgCl_2$ giving a final concentration of 1 mM per well

- 20 μ l of the assay mix are added per well.
- 2 mL 'Enzyme mix' are prepared per plate (x^* μ l PI3 kinase p110 β in 2 mL of kinase buffer). The 'Enzyme mix' is kept on ice during addition to the assay plates.
- 20 μ l 'Enzyme mix' are added/well to start the reaction.
- The plate is then incubated at room temperature for 90 minutes.
- The reaction is terminated by the addition of 50 μ l WGA-SPA bead (wheat germ agglutinin-coated Scintillation Proximity Assay beads) suspension per well.
- The assay plate is sealed using TopSeal-S (heat seal for polystyrene microplates, PerkinElmer LAS [Deutschland] GmbH, Rodgau, Germany) and incubated at room temperature for at least 60 minutes.
- The assay plate is then centrifuged at 1500 rpm for 2 minutes using the Jouan bench top centrifuge (Jouan Inc., Nantes, France).
- The assay plate is counted using a Packard TopCount, each well being counted for 20 seconds.

* The volume of enzyme is dependent on the enzymatic activity of the batch in use.

[0103] In a more preferred assay, the kinase reaction is performed in a final volume of 10 μ l per well of a low volume non-binding CORNING, 384 well black plate (Cat. No. #3676). The final concentrations of ATP and phosphatidyl inositol (PI) in the assay are 1 μ M and 10 μ g/mL, respectively. The reaction is started by the addition of ATP.

[0104] The components of the assay are added per well as follows:

50 nl test compounds in 90% DMSO per well, in columns 1-20, 8 concentrations (1/3 and 1/3.33 serial dilution step) in single.

- Low control: 50 nl of 90% DMSO in half the wells of columns 23-24 (0.45% in final).
- High control: 50 nl of reference compound (e.g. compound of Example 7 in WO 2006/122806) in the other half of columns 23-24 (2.5 μ M in final).
- Standard: 50 nl of reference compound as just mentioned diluted as the test compounds in columns 21-22.
- 20 mL 'buffer' are prepared per assay :

200 μ l of 1M TRIS HCl pH7.5 (10 mM in final)

60 μ l of 1M $MgCl_2$ (3 mM in final)

500 μ l of 2M NaCl (50 mM in final)

100 μ l of 10% CHAPS (0.05% in final)

200 μ l of 100mM DTT (1mM in final)

18.94 mL of nanopure water

- 10 mL 'PI' are prepared per assay :

200 μ l of 1 mg/mL I-alpha-Phosphatidylinositol (Liver Bovine, Avanti Polar Lipids Cat. No. 840042C MW=909.12) prepared in 3% OctylGlucoside (10 μ g/mL in final)

9.8 mL of 'buffer'

- 10 mL 'ATP' are prepared per assay :

6.7 μ l of 3 mM stock of ATP giving a final concentration of 1 μ M per well

10 mL of 'buffer'

- 2.5 μ L of each PI3K construct are prepared per assay in 'PI' with the following final concentration :

10 nM PI3K alfa EMV B1075

25 nM beta EMV BV949

10 nM delta EMV BV1060

150 nM gamma EMV BV950

- 5 μ l of 'PI/PI3K' are added per well.
- 5 μ l 'ATP' are added per well to start the reaction.
- The plates are then incubated at room temperature for 60 minutes (alfa, beta, delta) or 120 minutes (gamma).
- The reaction is terminated by the addition of 10 μ l Kinase-Glo (Promega Cat. No. #6714).
- The assay plates are read after 10 minutes in Synergy 2 reader (BioTek, Vermont USA) with an integration time of 100 milliseconds and sensitivity set to 191.
- Output: The High control is around 60'000 counts and the Low control is 30'000 or lower
- This luminescence assay gives a useful Z' ratio between 0.4 and 0.7

[0105] The Z' value is a universal measurement of the robustness of an assay. A Z' between 0.5 and 1.0 is considered an excellent assay.

[0106] For this assay, the PI3K constructs mentioned are prepared as follows:

1.2 Generation of gene constructs

[0107] Two different constructs, BV 1052 and BV 1075, are used to generate the PI3 Kinase α proteins for compound screening.

PI3K α BV-1052 p85(iSH2)-Gly linker-p110a(D20aa)-C-term His tag

[0108] PCR products for the inter SH2 domain (iSH2) of the p85 subunit and for the p110- α subunit (with a deletion of the first 20 amino acids) are generated and fused by overlapping PCR. The iSH2 PCR product is generated from first strand cDNA using initially primers

gwG130-p01 (5'-CGAGAATATGATAGATTATATGAAGAAT-3') (SEQ ID NO: 1) and gwG130-p02 (5'-TGGTTT-AATGCTGTTTCATACGTTTGTCAAT-3') (SEQ ID NO: 2).

[0109] Subsequently in a secondary PCR reaction, Gateway (Invitrogen AG, Basel, Switzerland) recombination AttB1 sites and linker sequences are added at the 5' end and 3' end of the p85 iSH2 fragment respectively, using primers

gwG130-p03 (5'- GGGACAAGTTTGTACAAAAAAGCAGGCTACGAAGGAGATATACATAT-GCGAGAATATGAT-AGATTATATGAAGAAT -3') (SEQ ID NO: 3) and
gwG152-p04 (5'- TACCATAATTCCACCACCACCACCGAAATTCCTGTTT-AATGCTGTTTCATACGTTT-GTCAAT-3') (SEQ ID NO: 4).

[0110] The p110-a fragment is also generated from first strand cDNA, initially using primers

gwG152-p01 (5'- CTAGTGAATGTTTACTACCAAATGG-3') (SEQ ID NO: 5) and
gwG152-p02 (5'- GTTCAATG-CATGCTGTTTAATTGTGT -3') (SEQ ID NO: 6).

[0111] In a subsequent PCR reaction, linker sequence and a Histidine tag are added at the 5' end and 3' end of the p110-a fragment respectively, using primers

[illegible]

(SEQ ID NO: 8).

[0112] The p85-iSH2/p110-a fusion protein is assembled in a third PCR reaction by the overlapping linkers at the 3' end of the iSH2 fragment and the 5' end of the p110-a fragment, using the above mentioned gwG130-p03 primer and a primer containing an overlapping Histidine tag and the AttB2 recombination sequences (5'-GGGACCACTTTGTACAAGAAAGCTGGGTTTAAGCTCCGTGATGGTGATGGTGAT-GTGCTCC-3') (SEQ ID NO: 9).

[0113] This final product is recombined in a (Invitrogen) OR reaction into the donor vector pDONR201 to generate the ORF318 entry clone. This clone is verified by sequencing and used in a Gateway LR reaction to transfer the insert into the Gateway adapted pBlueBac4.5 (Invitrogen) vector for generation of the baculovirus expression vector LR410.

PI3K α BV-1075 p85(iSH2)-12 XGly linker-p110a(D20aa)-C-term His tag

[0114] The construct for Baculovirus BV-1075 is generated by a three-part ligation comprised of a p85 fragment and a p110-a fragment cloned into vector pBlueBac4.5. The p85 fragment is derived from plasmid p1661-2 digested with Nhe/Spe. The p110-a fragment derived from LR410 (see above) as a SpeI/HindIII fragment. The cloning vector pBlueBac4.5 (Invitrogen) is digested with Nhe/HindIII. This results in the construct PED 153.8

[0115] The p85 component (iSH2) is generated by PCR using ORF 318 (described above) as a template and one forward primer

KAC1028 (5'- GCTAGCATGCGAGAATATGATAGATTATATGAAGAATATACC) (SEQ ID NO: 10) and two reverse primers,

KAC1029 (5'- GCCTCCACCACCTCCGCCTGGTTTAATGCTGTTTCATACGTTTGTC) (SEQ ID NO: 11) and

KAC1039 (5'-TACTAGTCCGCCTCCACCACCTCCGCCTCCACCACCTCCGCC) (SEQ ID NO: 12).

[0116] The two reverse primers overlap and incorporate the 12x Gly linker and the N-terminal sequence of the p110a gene to the SpeI site. The 12x Gly linker replaces the linker in the BV1052 construct. The PCR fragment is cloned into pCR2.1 TOPO (Invitrogen). Of the resulting clones, p1661-2 is determined to be correct. This plasmid is digested with Nhe and SpeI and the resulting fragment is gel-isolated and purified for sub-cloning.

[0117] The p110-a cloning fragment is generated by enzymatic digest of clone LR410 (see above) with Spe I and HindIII. The SpeI site is in the coding region of the p110a gene. The resulting fragment is gel-isolated and purified for sub-cloning.

[0118] The cloning vector, pBlueBac4.5 (Invitrogen) is prepared by enzymatic digestion with Nhe and HindIII. The cut vector is purified with Qiagen (Quiagen N.V, Venlo, Netherlands) column and then dephosphorylated with Calf Intestine alkaline phosphatase (CIP) (New England BioLabs, Ipswich, MA). After completion of the CIP reaction the cut vector is again column purified to generate the final vector. A 3 part ligation is performed using Roche Rapid ligase and the vendor specifications.

PI3K β BV-949 p85(iSH2)-Gly linker-p110b(full-length)-C-term His tag

[0119] PCR products for the inter SH2 domain (iSH2) of the p85 subunit and for the full-length p110-b subunit are generated and fused by overlapping PCR.

[0120] The iSH2 PCR product is generated from first strand cDNA initially using primers

gwG130-p01 (5'-CGAGAATATGATAGATTATATGAAGAAT-3') (SEQ ID NO: 1) and

gwG130-p02 (5'-TGGTTT-AATGCTGTTTCATACGTTTGTC-3') (SEQ ID NO: 2).

[0121] Subsequently, in a secondary PCR reaction Gateway (Invitrogen) recombination AttB1 sites and linker sequences are added at the 5' end and 3' end of the p85 iSH2 fragment respectively, using primers

gwG130-p03 (5'-GGGACAAAGTTTGTACAAAAAGCAGGCTACGAAGGAGATA-TACATATGCGAGAATATGAT-AGATTATATGAAGAAT-3') (SEQ ID NO: 3) and

gwG130-p05 (5'-ACTGAAGCATCCTCCTCCTCCTCCTGTTTAAT-GCTGTTTCATACGTTTGTC-3') (SEQ ID NO: 13).

[0122] The p110-b fragment is also generated from first strand cDNA initially using primers

gwG130-p04 (5'-ATTAAACCAGGAGGAGGAGGAGGAGGATGCTTCAGTTTCATAATGCC-TCCTGCT -3') (SEQ

ID NO: 4)

which contains linker sequences and the 5'end of p110-b and

5 gwG130-p06 (5'-AGCTCCGTGATGGTGATGGTGATGTGCTCCAGATCTGTAGTCTTT-CCGAAGTGTGTG -3')
(SEQ ID NO: 14)

which contains sequences of the 3'end of p110-b fused to a Histidine tag.

10 **[0123]** The p85-iSH2/p110-b fusion protein is assembled by an overlapping PCR a reaction of the linkers at the 3'end of the iSH2 fragment and the 5'end of the p110-b fragment, using the above mentioned gwG130-p03 primer and a primer containing an overlapping Histidine tag and the AttB2 recombination sequences (5'-GGGACCACTTTGTACAA-GAAAGCTGGGTTT-AAGCTCCGTGATGGTGATGGTGATGTGCTCC-3') (SEQ ID NO: 15).

15 **[0124]** This final product is recombined in a Gateway (Invitrogen) OR reaction into the donor vector pDONR201 to generate the ORF253 entry clone. This clone is verified by sequencing and used in a Gateway LR reaction to transfer the insert into the Gateway adapted pBlueBac4.5 (Invitrogen) vector for generation of the baculovirus expression vector LR280.

PI3K δ BV-1060 p85(iSH2)-Gly linker-p110d(full-length)-C-term His tag

20 **[0125]** PCR products for the inter SH2 domain (iSH2) of the p85 subunit and for the full-length p110-d subunit are generated and fused by overlapping PCR.

25 **[0126]** The iSH2 PCR product is generated from first strand cDNA using initially primers gwG130-p01 (5'-CGAGAATAT-GATAGATTATATGAAGAAT-3') (SEQ ID NO: 1) and gwG130-p02 (5'-TGGTTT-AATGCTGTTTCATACGTTTGTCAAT-3') (SEQ ID NO: 2). Subsequently, in a secondary PCR reaction Gateway (Invitrogen) recombination AttB1 sites and linker sequences are added at the 5'end and 3'end of the p85 iSH2 fragment respectively, using primers

gwG130-p03 (5'- GGGACAAGTTTGTACAAAAAAGCAGGCTACGAAGGAGATATACAT-ATGCGAGAATATGAT-AGATTATATGAAGAAT -3') (SEQ ID NO: 3) and

30 gwG154-p04 (5'- TCCTCCTCCTCCTCCTGTTTAATGCTGTTCATACGTTTGTC -3') (SEQ ID NO: 16).

[0127] The p110-a fragment is also generated from first strand cDNA using initially primers gwG154-p01 (5'- AT-GCCCCCTGGGGTGGACTGCCCCAT -3') (SEQ ID NO: 17) and gwG154-p02 (5'- CTAAGT-CCTGTTGTCTTT-GGACACGT -3') (SEQ ID NO: 18).

35 **[0128]** In a subsequent PCR reaction linker sequences and a Histidine tag is added at the 5'end and 3'end of the p110-d fragment respectively, using primers gw154-p03 (5'- ATTAACCCAGGAGGAGGAGGAGGAGGAGGACCCCCCTGGGGTGGAC-TGCCCCATGGA -3') (SEQ ID NO: 19) and gwG154-p06 (5'-AGCTCCGTGATGGTGAT-GGTGATGTGCT-CCCTGCCTGTTGTCTTTGGACACGTT-GT -3') (SEQ ID NO: 20).

40 **[0129]** The p85-iSH2/p110-d fusion protein is assembled in a third PCR reaction by the overlapping linkers at the 3'end of the iSH2 fragment and the 5'end of the p110-d fragment, using the above mentioned gwG130-p03 primer and a primer containing an overlapping Histidine tag and the Gateway (Invitrogen) AttB2 recombination sequences (5'-GGGACCACTTTGTA-CAAGAAAGCTGGGTTT-AAGCTCCGTGATGGTGATGGTGATGTGCTCC-3') (SEQ ID NO: 21).

45 **[0130]** This final product is recombined in a Gateway (Invitrogen) OR reaction into the donor vector pDONR201 to generate the ORF319 entry clone. This clone is verified by sequencing and used in a Gateway LR reaction to transfer the insert into the Gateway adapted pBlueBac4.5 (Invitrogen) vector for generation of the baculovirus expression vector LR415.

PI3K γ BV-950 p110g(D144aa)-C-term His tag

50 **[0131]** This construct is obtained from Roger Williams lab, MRC Laboratory of Molecular Biology, Cambridge, UK (November, 2003). Description of the construct in: Pacold M. E. et al. (2000) Cell 103, 931-943.

1.3 Protein expression and purification

55 **[0132]** Methods to generate recombinant baculovirus and protein for PI3K isoforms:

The pBlue-Bac4.5 (for a, b, and d isoforms) or pVL1393 (for g) plasmids containing the different PI3 kinase genes

are co-transfected with BaculoGold WT genomic DNA (BD Biosciences, Franklin Lakes, NJ, USA) using methods recommended by the vendor.

[0133] Subsequently, the recombinant baculovirus obtained from the transfection is plaque-purified on Sf9 insect cells to yield several isolates expressing recombinant protein. Positive clones are selected by anti-HIS or anti-isoform antibody western. For PI3K alpha and delta isoforms, a secondary plaque-purification is performed on the first clonal virus stocks of PI3K. Amplification of all baculovirus isolates is performed at low multiplicity of infection (moi) to generate high-titer, low passage stock for protein production. The baculoviruses are designated BV1052 (α) and BV1075 (α), BV949 (β), BV1060 (δ) and BV950 (γ).

[0134] Protein production involves infection (passage 3 or lower) of suspended Tn5 (*Trichoplusia ni*) or TiniPro (Expression Systems, LLC, Woodland, CA, USA) cells in protein-free media at moi of 2-10 for 39-48 hours in 2 l glass Erlenmeyer flasks (110 rpm) or wave-bioreactors (22-25 rpm). Initially, 10 l working volume wave-bioreactors are seeded at a density of 3e5 cells/mL at half capacity (5L). The reactor is rocked at 15 rpm during the cell growth phase for 72 hours, supplemented with 5% oxygen mixed with air (0.2 l per minute). Immediately prior to infection, the wave-reactor cultures are analyzed for density, viability and diluted to approximately 1.5e6 cell/mL. 100-500 mL of high titer, low passage virus is added following 2-4 hours of additional culture. Oxygen is increased to 35% for the 39-48 hour infection period and rocking platform rpm increased to 25. During infection, cells are monitored by Vicell viability analyzer (Beckman Coulter, Inc, Fullerton, CA, USA) bioprocess for viability, diameter and density. Nova Bioanalyzer (NOVA Biomedical Corp., Waltham, MA, USA) readings of various parameters and metabolites (pH, O₂ saturation, glucose, etc.) are taken every 12-18 hours until harvest. The wave-bioreactor cells are collected within 40 hours post infection. Cells are collected by centrifugation (4 degrees C at 1500 rpm), and subsequently maintained on ice during pooling of pellets for lysis and purification. Pellet pools are made with small amounts of cold, un-supplemented Grace's media (w/o protease inhibitors).

PI3K alpha Purification Protocol For HTS (BV1052)

[0135] PI3K alpha is purified in three chromatographic steps: immobilized metal affinity chromatography on a Ni Sepharose resin (GE Healthcare, belonging to General Electric Company, Fairfield, CT, USA), gel filtration utilizing a Superdex 200 26/60 column (GE Healthcare), and finally a cation exchange step on a SP-XL column (GE Healthcare). All buffers are chilled to 4°C and lysis is performed chilled on ice. Column fractionation is performed rapidly at room temperature.

[0136] Typically frozen insect cells are lysed in a hypertonic lysis buffer and applied to a prepared IMAC column. The resin is washed with 3-5 column volumes of lysis buffer, followed by 3-5 column volumes wash buffer containing 45 mM imidazole, and the target protein is then eluted with a buffer containing 250 mM imidazole. Fractions are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled and applied to a prepared GFC column. Fractions from the GFC column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled. The pool from the GFC column is diluted into a low salt buffer and applied to a prepared SP-XL column. The column is washed with low salt buffer until a stable A280 baseline absorbance is achieved, and eluted using a 20 column volume gradient from 0 mM NaCl to 500 mM NaCl. Again, fractions from the SP-XL column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing the target protein are pooled. The final pool is dialyzed into a storage buffer containing 50% glycerol and stored at -20°C. The final pool is assayed for activity in a phosphoinosititol kinase assay.

PI3K beta Purification Protocol For HTS (BV949)

[0137] PI3K beta is purified in two chromatographic steps: immobilized metal affinity chromatography (IMAC) on a Ni Sepharose resin (GE Healthcare) and gel filtration (GFC) utilizing a Superdex 200 26/60 column (GE Healthcare). All buffers are chilled to 4°C and lysis is performed chilled on ice. Column fractionation is performed rapidly at room temperature.

[0138] Typically frozen insect cells are lysed in a hypertonic lysis buffer and applied to a prepared IMAC column. The resin is washed with 3-5 column volumes of lysis buffer, followed by 3-5 column volumes wash buffer containing 45 mM imidazole, and the target protein is then eluted with a buffer containing 250 mM imidazole. Fractions are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled and applied to a prepared GFC column. Fractions from the GFC column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled. The final pool is dialyzed into a storage buffer containing 50% glycerol and stored at -20°C. The final pool is assayed for activity in the phosphoinosititol kinase assay.

PI3K gamma Purification Protocol For HTS (BV950)

[0139] PI3K gamma is purified in two chromatographic steps: immobilized metal affinity chromatography (IMAC) on a Ni Sepharose resin (GE Healthcare) and gel filtration (GFC) utilizing a Superdex 200 26/60 column (GE Healthcare). All buffers are chilled to 4°C and lysis is performed chilled on ice. Column fractionation is performed rapidly at room temperature. Typically frozen insect cells are lysed in a hypertonic lysis buffer and applied to a prepared IMAC column. The resin is washed with 3-5 column volumes of lysis buffer, followed by 3-5 column volumes wash buffer containing 45 mM imidazole, and the target protein is then eluted with a buffer containing 250 mM imidazole. Fractions are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled and applied to a prepared GFC column. Fractions from the GFC column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled. The final pool is dialyzed into a storage buffer containing 50% glycerol and stored at -20°C. The final pool is assayed for activity in the phosphoinositol kinase assay.

PI3K delta Purification Protocol For HTS (BV1060)

[0140] PI3K delta is purified in three chromatographic steps: immobilized metal affinity chromatography on a Ni Sepharose resin (GE Healthcare), gel filtration utilizing a Superdex 200 26/60 column (GE Healthcare), and finally a anion exchange step on a Q-HP column (GE Healthcare). All buffers are chilled to 4°C and lysis is performed chilled on ice. Column fractionation is performed rapidly at room temperature. Typically frozen insect cells are lysed in a hypertonic lysis buffer and applied to a prepared IMAC column. The resin is washed with 3-5 column volumes of lysis buffer, followed by 3-5 column volumes wash buffer containing 45 mM imidazole, and the target protein is then eluted with a buffer containing 250 mM imidazole. Fractions are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing the target protein are pooled and applied to a prepared GFC column. Fractions from the GFC column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing the target protein are pooled. The pool from the GFC column is diluted into a low salt buffer and applied to a prepared Q-HP column. The column is washed with low salt buffer until a stable A280 baseline absorbance is achieved, and eluted using a 20 column volume gradient from 0 mM NaCl to 500 mM NaCl. Again, fractions from the Q-HP column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing the target protein are pooled. The final pool is dialyzed into a storage buffer containing 50% glycerol and stored at -20°C. The final pool is assayed for activity in the phosphoinositol kinase assay.

IC₅₀ is determined by a four parameter curve fitting routine that comes along with "excel fit". A four parameter logistic equation is used to calculate IC₅₀ values (IDBS XLfit) of the percentage inhibition of each compound at 8 concentrations (usually 10, 3.0, 1.0, 0.3, 0.1, 0.030, 0.010 and 0.003 μM). Alternatively, IC₅₀ values are calculated using idbsXLfit model 204, which is a 4 parameter logistic model.

[0141] Yet alternatively, for an ATP depletion assay, the PI3K inhibitors, wherein said inhibitors have an inhibitory action on the PI3K isoform delta, to be tested are dissolved in DMSO and directly distributed into a white 384-well plate at 0.5 μl per well. To start the reaction, 10 μl of 10 nM PI3 kinase and 5 μg/mL 1-alpha-phosphatidylinositol (PI) are added into each well followed by 10 μl of 2 μM ATP. The reaction is performed until approx 50% of the ATP is depleted, and then stopped by the addition of 20 μl of Kinase-Glo solution (Promega Corp., Madison, WI, USA). The stopped reaction is incubated for 5 minutes and the remaining ATP is then detected via luminescence. IC₅₀ values are then determined.

[0142] Some of the compounds of examples 1-49 and 51-95 show a certain level of selectivity against the different paralogs PI3K α, β, γ and δ.

Suitably, the compounds of examples 1-49 and 51-95 show a certain level of selectivity for the isoform PI3Kδ, e.g. as indicated in in vitro and in vivo tests against the different paralogs PI3K α and β.

Some of the compounds of examples 1'-117' show a certain level of selectivity against the different paralogs PI3K α, β, γ and δ.

Suitably, the compounds of examples 1'-117' show a certain level of selectivity for the isoform PI3Kδ e.g. as indicated in in vitro and in vivo tests with selectivity of at least 10-fold, and more preferably at least 30-fold against the different paralogs PI3K α and β.

[0143] The range of activity, expressed as IC₅₀, in these assays, is preferably between 1 nM and 5000 nM, more preferably between 1 nM and about 1000 nM.

2. Cellular assays**2.1 Determination of PI3K alpha, PI3K beta and PI3K delta inhibition in Rat1 cells**

[0144] The efficacy of the compounds in blocking the activation of the PI3K/Akt pathway was demonstrated in cellular settings using a homogeneous sandwich phospho-ELISA based on the ALPHA technology of Perkin Elmer for a sensitive

quantification of compound of mediated inhibition of Akt Ser473 phosphorylation in Rat1 cells stably transfected with activated versions of PI3-kinase isoforms alpha, beta or delta:

2.1.1 Cells and cell culture conditions

[0145] Rat1 cell lines stably expressing a myr-HA-tagged, constitutively active subunit of the human catalytic PI3K class I p110 isoform α , β or δ (addition of a myristylation signal at the N-terminus of p110 isoforms has been shown to lead to constitutive activation of PI3K and corresponding downstream signals, such as phosphorylation of Akt at Ser473) were cultivated in Dulbecco's modified Eagle's medium (DMEM high Glucose, GIBCO, cat. No. 41956-039) supplemented with 10% heat inactivated fetal bovine calf serum (Amimed, cat. No. 2-01F16-I), 1% L-Glutamine (Invitrogen, cat. No. 25030-02), 1% penicillin-streptomycin (GIBCO, cat. No. 15140-114) and 10 μ g/ml Puromycin (Sigma, cat. No. P9620).

2.1.2 Compound treatment of cells and preparation of samples

[0146] The Rat1-myr-HA-p110 alpha, beta and delta cells were trypsinized and counted with a CASY TT cell counter (Schärfe System GmbH, Reutlingen Germany). Rat cell expressing the catalytic subunit of human phosphoinositide-3 kinase (PI3K) myr-HA-p110 alpha, beta and delta were seeded in 384-well plates at a density of 7500 (PI3K alpha), 6200 (PI3K beta), or 4000 (PI3K delta) cells in 40ul complete growth medium (Dulbecco's modified Eagle's medium (DMEM high glucose) supplemented with 10% (v/v) fetal bovine serum, 1% (v/v) MEM non essential amino acids, 10mM HEPES, 2mM L-glutamine, 10 μ g/mL puromycin and 1% (v/v) Penicillin/Streptomycin) and were incubated at 37°C / 5%CO₂ / 95% humidity for 48-72 h before exposing them to test compounds.

[0147] The compounds were prepared as 10 mM stock solutions in 90% DMSO (Merck, # 8.02912.2500) in 384 well plates (Greiner PP-Microplate, #781201) in 3-fold serial dilutions in 90 % DMSO (Merck, #8.02912.2500) with 8 concentrations starting at 10 mM. Compounds were diluted in 384-well compound plates to obtain 8-point serial dilutions for 40 test, as well as 4 reference compounds plus 16 high controls and 16 low (inhibited) controls. Predilution plates were prepared by dispensing 250 nl of each compound solutions into 384-well polypropylen plates using a Hummingwell nanoliter dispenser. Compounds were then further diluted by the addition of 49.75 ul complete growth medium. 10ul of prediluted compound solution were transferred to the cell plate using a 384-well pipettor, resulting in a final volume of 50 ul and a DMSO concentration of 0.11% including for the control cells (high and low control). The compound dilution resulted in the above specified 8 final concentrations of 10, 3.333, 1.111, 0.370, 0.123, 0.041, 0.014 and 0.005 μ M

2.1.3 Phosphoinositide-3 kinase (PI3K)-mediated Akt 1/2 (S473) phosphorylation in Rat-1 cells

[0148] For detection of p-Akt(Ser473), the SureFire® p-Akt 1/2 (Ser473) Assay Kit (PerkinElmer, U.S.A) was used. Untreated cells were used as low controls, cells stimulated in absence of compounds were used as high controls. After an incubation of 1h with compounds at 37°C / 5%CO₂ / 95% humidity, cells were lysed by addition of 20ul of lysis buffer for AlphaScreen® SureFire® detection enriched with 0.72 % BSA. Cell lysates were either used immediately or stored frozen (in sealed plates) at -20°C until use.

[0149] Five ul of cell lysate was transferred to 384-well low volume Proxiplates for detection using a 384-well pipettor. Addition of AlphaScreen® SureFire® reagents was done according to the manufacturer's protocol. First, 5ul of reaction buffer plus activation buffer mix containing AlphaScreen® acceptor beads was added, the plate was sealed, and incubated on a plate shaker for 2 hours at room temperature. Second, 2ul of dilution buffer containing AlphaScreen® donor beads was added, and the plate was incubated on plate shaker as above for a further 2 hours in the dark at RT. Then light emission was measured using the EnVision Reader (Perkin Elmer). The difference between high and low controls was taken as 100 % and compound effects were expressed as percent inhibition. IC₅₀ values were determined from the dose response curves by graphical extrapolation.

2.2 Determination of TLR9-induced IL-6 in murine splenocytes

2.2.1 Preparation of single cell suspension from mouse spleen

[0150] Spleens were dissected from C57BL/6 mice immediately following euthanasia. Excess fat was trimmed from the spleens prior to mashing the spleen through a 0.4 μ M cell strainer using a plunger from a 5 ml syringe. A single cell suspension was prepared and the volume was adjusted to 15 ml in a 50 ml Falcon tube using cold PBS. Cells were centrifuged at 1500 rpm for 5 minutes at 4°C degrees prior to removal of supernatant and re-suspension in 5 ml of red blood cell lysis buffer per spleen and incubation for 5 minutes at room temperature. Ice cold PBS (30 ml) was added to the cells prior to centrifugation at 1500 rpm for 5 minutes at 4°C. The supernatant was removed and the cells were washed twice with 40 ml of murine splenocyte culture media (MSCM). MSCM consisted of RPMI supplemented with

100 units/ml Penicillin and 100 µg/ml Streptomycin, 1 x nonessential amino acids, 1 mM Sodium Pyruvate, 0.05 mM β-mercaptoethanol, and 10 % heatinactivated Fetal Bovine Serum (FBS). Cells were re-suspended in 10-20 ml of MSCM and counted using a Countess cell counter. Approximately 60x10⁶ splenocytes were obtained from a single C57BL/6 mouse spleen.

2.2.2 Stimulation of C57BL/6 murine splenocytes and treatment with specific inhibitor

[0151] Splenocytes were plated at a final density of 2x10⁵ cells/well in a volume of 100 µl in 96 well flat bottomed plates and incubated in a humidified 37°C incubator for 2-4 hours. Afterwards, compounds to be tested were dispensed using an automated liquid handling machine using previously prepared compound stock plates. Stock plates consisted of compounds (in 90%/10% DMSO/ddH₂O) arrayed in 9 point using 3-fold dilutions. The liquid handling machine dispensed 1 µl of each dilution from the previously prepared compound source plate into the appropriate destination well in the 96-well plate. The final starting concentration of the compounds in the cell culture was 10 µM. The final concentration of DMSO in the cell cultures was 0.5%. Cells were incubated with compounds for 1 hour prior to addition of TLR ligand. Then, a 10x EC₈₀ concentration of CpG1826 was added in a volume of 20 µl (for a final culture volume of 200 µl) whereupon cultures were incubated overnight in a humidified 37°C incubator.

2.2.3 Determination of Interleukin-6 by ELISA

[0152] After overnight culture, cells were transferred to 96-well V-bottomed plates and centrifuged at 2000 rpm for 5 minutes at room temperature. Subsequently 150 µl of each culture supernatant was transferred to 96-well flat-bottomed plates and IL-6 levels were measured using commercially available mouse IL-6 sandwich ELISA kit (R&D systems). Briefly, plates were coated overnight with the capture antibody prior to blocking for 1 hour with PBS/0.1 % BSA. Samples and standards were added in a volume of 50 µl and the plate was incubated for 2 hours at room temperature. After removal of the standards/samples, the plate was washed using PBS/0.05% Tween prior to addition of 50 µl of the biotinylated detection antibody whereupon the plate was incubated for 2 hours at room temperature with agitation. Plates were washed again using PBS/0.05% Tween prior to addition of 50 µl streptavidin-horseradish peroxidase per well for 20 minutes. Following additional plate washes 50 µl TMB substrate was added to each well and plates were incubated for 20 minutes prior addition of 25 µl/well stop solution. IL-6 levels were measured using a SpectraMax 190 Plate Reader (450 nm) and analyzed using SoftMax Pro and GraphPad Prism software.

2.3 Determination of TLR9-induced IFN-alpha in murine splenocytes

2.3.1 Preparation of single cell suspension from mouse spleen

[0153] Spleens were dissected from 129/Sv mice immediately following euthanasia. Excess fat was trimmed from the spleens prior to mashing the spleen through a 0.4 µM cell strainer using a plunger from a 5 ml syringe. A single cell suspension was prepared and the volume was adjusted to 15 ml in a 50 ml Falcon tube using cold PBS. Cells were centrifuged at 1500 rpm for 5 minutes at 4°C degrees prior to removal of supernatant and re-suspension in 5 ml of red blood cell lysis buffer per spleen and incubation for 5 minutes at room temperature. Ice cold PBS (30 ml) was added to the cells prior to centrifugation at 1500 rpm for 5 minutes at 4°C. The supernatant was removed and the cells were washed twice with 40 ml of murine splenocyte culture media (MSCM). MSCM consisted of RPMI supplemented with 100 units/ml Penicillin and 100 µg/ml Streptomycin, 1 x nonessential amino acids, 1 mM Sodium Pyruvate, 0.05 mM β-mercaptoethanol, and 10 % heatinactivated Fetal Bovine Serum (FBS). Cells were re-suspended in 10-20 ml of MSCM and counted using a Countess cell counter. Approximately 60x10⁶ splenocytes were obtained from a single C57BL/6 mouse spleen.

2.3.2 Stimulation of 129/Sv murine splenocytes and treatment with specific inhibitor

[0154] Splenocytes were plated at a final density of 2x10⁵ cells/well in a volume of 100 µl in 96 well flat bottomed plates and incubated in a humidified 37°C incubator for 2-4 hours. Afterwards, compounds to be tested were dispensed using an automated liquid handling machine using previously prepared compound stock plates. Stock plates consisted of compounds (in 90%/10% DMSO/ddH₂O) arrayed in 9 point using 3-fold dilutions. The liquid handling machine dispensed 1 µl of each dilution from the previously prepared compound source plate into the appropriate destination well in the 96-well plate. The final starting concentration of the compounds in the cell culture was 10 µM. The final concentration of DMSO in the cell cultures was 0.5%. Cells were incubated with compounds for 1 hour prior to addition of TLR ligand. Then, a 10x EC₈₀ concentration of CpG1585 was added in a volume of 20 µl (for a final culture volume of 200 µl) whereupon cultures were incubated overnight in a humidified 37°C incubator.

2.3.3 Determination of IFN- α by ELISA

[0155] After overnight culture, cells were transferred to 96-well V-bottomed plates and centrifuged at 2000 rpm for 5 minutes at room temperature. Subsequently 150 μ l of each culture supernatant was transferred to 96-well flat-bottomed plates and IL-6 levels were measured using commercially available mouse IFN- α sandwich ELISA kit (PBL Interferon Source). Briefly, pre-coated plates were incubated 1 hour with 100 μ l standards/samples and 50 μ l detection antibody solution under gently shaking, prior 24 hours incubation at 4 degrees without shaking. The plates were then washed using PBS/0.05% Tween prior to addition of 100 μ l streptavidin-horseradish peroxidase per well for 2 hours at room temperature with gently shaking. Following a new washing step, 100 μ l TMB substrate was added to each well and plates were incubated for 15 minutes (in the dark and without shaking), prior addition of 100 μ l/well stop solution. IFN- α levels were measured within 5 minutes using a SpectraMax 190 Plate Reader (450 nm) and analyzed using SoftMax Pro and GraphPad Prism software.

2.4 Determination of TLR9-induced IFN α in human peripheral blood mononuclear cells (PBMCs) and isolated plasmacytoid dendritic cells (pDCs)

2.4.1 Preparation of PBMC from fresh human blood

[0156] Human blood (ca. 75 ml) was collected in 10 S-Monovette tubes containing Heparin (S-Monovette 7.5 mL NH Heparin 16 IU/mL blood; Starstedt). Leucosep™ tubes (30 mL #227290; Greiner Bio-one) were prepared by addition of 15 ml lymphocyte separation medium LSM1077™ per tube (#J15-004; PAA Laboratories) and centrifugation for 30 sec at 1000g. Some 25 ml blood was transferred to Leucosep™ tubes following dilution with equal parts of PBS (without Ca²⁺/Mg²⁺; #14190-094). Samples were centrifuged at 800g for 20 min at 22 °C using an Eppendorf 5810R centrifuge without brake. The PBMC layer was carefully removed from plasma:separation medium interface and transferred into clean 50 ml tube. Cells were washed once by addition of PBS (up to 45 ml) and centrifuged (1400rpm, 10 min at 22 °C) with brake (set at speed 9) using an Eppendorf 5810R. Pelleted cells were carefully resuspended in Media (RPMI 1640+GlutaMAX-I, 0.05 mM 2-mercaptoethanol, 10 mM HEPES and 5% v/v FCS) and samples pooled. The medium components 2-mercaptoethanol (#31350-010; 50 mM), Hepes (#15630-056, 1M) and RPMI 1640 (1x) + GlutaMAX-I (#61870-010) were obtained from Gibco. FCS (#2-01 F36-1) was obtained from Amimed. The PBMC were counted using a Countess® Automated cell counter (sample was pre-diluted 1:10 in Media, prior to the addition of equal volume (10 μ l) of Trypan Blue). Cells were diluted to 4 x 10⁶ cells/ml and seeded in 384-well plates (#353962; Becton Dickinson AG) to give a final volume of 25 μ l (i.e. 1 x 10⁵ cells/well).

2.4.2 Isolation of fresh human pDCs from Buffy Coats/PBMCs

[0157] Human PBMCs were prepared using Buffy Coats as source material from healthy donations (approx. 50 ml obtained from Blutspendezentrum SRK Basel) and processed as indicated above. Fresh PBMCs were resuspended and diluted in RoboSep™ buffer (PBS containing 2% v/v FBS, 1 mM EDTA (Gibco #15575-038) to obtain a final concentration of 50 x 10⁶ PBMCs/ml. Human pDCs (negative selection) were isolated using plasmacytoid DC Enrichment kit (Stemcell, #19062) using an automation RobSep™ station as described according to manufacturer protocols. Typical pDC yields were approx. 0.1% of total PBMCs and with a purity >90%. Isolated pDCs were diluted to 4 x 10⁵ cells/ml and seeded in 384-well plates (#353962; Becton Dickinson AG) to give a final volume of 25 μ l (i.e. 1 x 10⁴ cells/well). For stimulation using malaria nuclear extract (see below), pDCs were seeded at a final concentration of 5 x 10⁴ cells/well.

2.4.3 Preparation of Plasmodium falciparum nuclear extract

[0158] The preparation of the nuclear extract of plasmodium falciparum was performed according to Gowda et al [Gowda et al. "The Nucleosome (Histone-DNA Complex) Is the TLR9-Specific Immunostimulatory Component of Plasmodium falciparum That Activates DCs", PLoS ONE 2011]. In brief, Plasmodium falciparum 3D7 parasites were cultured in human red blood cell at 2% hematocrit. When the parasite was at late trophozoite and schizont stages, the infected red blood cells (IRBCs) were harvested by centrifugation and the pellets were re-suspended in 20 volumes of 0.1% saponin (m/v) in PBS, pH 7.2. The re-suspension was incubated on ice for 10 minutes and centrifuged at 2,500 g at 4°C for 15 min. The pellet was re-suspended in the above solution, incubated on ice for 10 min and centrifuged at 2,500 g at 4°C for 15 min. The parasite pellet thus obtained was washed 3 times with cold PBS, pH 7.2, by centrifugation. Each time 35ml of cold PBS was used. The pellet obtained after the last centrifugation was suspended in 10 volumes of lysis buffer (20 mM HEPES, pH 7.5, 10 mM KCl, 1 mM EDTA, 1 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride (PMSF) and 1% Triton X-100) and incubated on ice for 5 min. The suspension was centrifuged at 5,000 g at 4°C for 10 min, and nuclear material was washed three times with the lysis buffer to remove membrane components. The nuclear material

was re-suspended in PBS, pH 7.2. Insoluble material was subsequently solubilized by using a water-bath sonicator.

2.4.4 Stimulation of PBMC or pDCs and treatment with specific inhibitor

[0159] Compounds were pre-diluted in 100 % v/v DMSO (#41640-100mL; Sigma-Aldrich), followed by transfer in Media (to achieve a final DMSO concentration of 0.25 %). Cells were treated with appropriate compound dilution (5 μ l) or vehicle control (5 μ l) and incubated for 30 min at 37 °C in a humidified incubator in air with 5 % (v/v) CO₂. Cells were stimulated with CpG2216 (0.3 μ M; #tlrl-hodna; Invivogen), malaria nuclear extract (2.5 μ g/ml; see above for preparation) or vehicle control (10 μ l/well) and incubated for 20 h. Plates were briefly centrifuged (200 x g for 2 min at 22 °C) and supernatant samples (30 μ l) removed for quantification of IFN α levels.

2.4.5 Quantification of IFN α using AlphaLisa technology

[0160] For quantification of IFN α the human interferon AlphaLISA Kit (#AL264F) from PerkinElmer was used. An antibody mix containing anti-IFN α acceptor beads (5 μ g/ml final) and biotinylated antibody anti-IFN α (0.5 nM final) is prepared fresh and dispensed (5 μ l) into 384-well Optiplates™ (#6007299; PerkinElmer). Dilution of known IFN α standards (human IFN α B (2b)) were prepared and together with cell supernatants (5 μ l) were added to plates above. Plates were briefly centrifuged (pulse at 200g), covered with adhesive sealing film, vortexed and incubated 1 h at room temperature in the dark. Streptavidin-coated donor beads (20 μ g/ml final) was prepared and added to each well (5 μ l) in a dark lit area (light sensitive mix). Plates were incubated 30 min at room temperature (Plates must not be centrifuged or covered). After incubation, the plates were read with an EnVision™ multiplate reader equipped with the ALPHA option using the instrument's own "AlphaScreen standard settings" (e.g. total measurement time: 550 ms, Laser 680 nm excitation time: 180 ms, mirror: D640 as, emission filter: M570w, center wavelength 570 nm, bandwidth 100 nm, transmittance 75%). Data were collected for analysis and quantification of IFN α levels.

2.4.6 Data evaluation and analysis

[0161] Data were analysed using Excel XL fit 4.0 (Microsoft) with XLfit add-in (IDBS; version 4.3.2). Specific IFN α concentrations were determined following extrapolation to standard curves using human IFN α B (2b). Individual IC₅₀ values of compounds were determined by nonlinear regression after fitting of curves to the experimental data.

Biological data

[0162]

Enzymatic Assay

Example	PI3K alpha (uM)	PI3K delta (uM)
1	2.0378	0.015
2	3.391	0.009
3	2.386	0.015
4	1.764	0.033
5	0.749	0.020
6	0.987	0.044
7	1.973	0.013
8	2.494	0.027
9	2.906	0.009
10	0.668	0.009
11	1.199	0.011
12	0.952	0.012
13	1.802	0.013
14	1.832	0.013

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(continued)

5

10

15

20

25

30

35

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45

50

55

Example	PI3K alpha (uM)	PI3K delta (uM)
15	1.631	0.014
16	1.684	0.016
17	7.678	0.017
18	0.871	0.033
19	3.056	0.033
20	1.839	0.048
21	0.320	0.008
22	0.580	0.008
23	0.129	0.010
24	0.374	0.009
25	0.820	0.026
26	0.368	0.021
27	3.410	0.040
28	1.214	0.004
29	2.585	0.011
30	2.831	0.040
31	3.024	0.021
32	2.036	0.023
33	1.967	0.018
34	1.648	0.014
35	4.232	0.049
36	4.103	0.025
37	7.021	0.031
38	3.306	0.016
39	0.434	0.009
40	0.260	0.006
41	0.515	0.014
42	0.863	0.013
43	0.728	0.016
44	1.189	0.016
45	0.860	0.018
46	0.803	0.027
47	0.656	0.025
48	0.518	0.029
49	0.388	0.034
51	0.912	0.044
52	1.024	0.046
53	0.504	0.006

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(continued)

Example	PI3K alpha (uM)	PI3K delta (uM)
54	0.384	0.005
55	0.661	0.005
56	0.860	0.013
57	0.590	0.025
58	3.060	0.030
59	9.100	0.028
60	3.333	0.045
61	0.589	0.012
62	0.489	0.023
63	0.791	0.051
64	2.331	0.032
65	0.738	0.023
66	1.280	0.014
67	0.262	0.023
68	0.043	0.007
69	0.056	0.003
70	0.121	0.006
71	0.057	0.003
72	0.093	0.004
73	0.054	0.004
74	0.113	0.004
75	0.118	0.004
76	0.106	0.007
77	1.290	0.044
78	0.384	0.012
79	0.781	0.017
80	0.430	0.016
81	0.651	0.02
82	0.066	0.003
83	0.432	0.017
84	0.058	0.009
85	0.569	0.021
86	1.330	0.020
87	0.452	0.012
88	1.336	0.034
89	1.189	0.029
90	1.991	0.038
91	0.924	0.011

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(continued)

Example	PI3K alpha (uM)	PI3K delta (uM)
92	2.545	0.009
93	0.872	0.024
94	1.714	0.021
95	0.757	0.053

Cellular Assays

[0163]

PI3K delta inhibition in Rat1-myr-HA-p110 delta cells

Example	Cell PI3K δ / IC ₅₀ [umol I-1]
1	0.153
5	0.455
20	0.254
28	0.268
65	0.191
67	0.047
68	0.053
71	0.035
81	0.246
82	0.116

Inhibition of TLR9-induced cytokine production in murine splenocytes

Example	TLR9-ligand induced IL-6 in murine splenocytes	TLR9-ligand induced IFN α in murine splenocytes
	IC ₅₀ [microM]	IC ₅₀ [microM]
1	0.327 (n=2)	nd
67	0.096 (n=2)	>2.220 (n=2)

Inhibition of TLR9-induced cytokine production in human PBMC and pDCs

Example	TLR9-ligand induced IFN α in human PBMC	TLR9-ligand induced IFN α in human pDCs
	IC ₅₀ [umol I-1]	IC ₅₀ [umol I-1]
1	0.211 (n=3)	0.050 (n=4)
67	0.109 (n=3)	0.033 (n=4)

Inhibition of *P.falciparum* nuclear extract-induced cytokine production in human pDCs

Example	Condition (isolated human pDCs)	IFN α level [pg/ml]	% inh.of IFN α by nuclear extract
	vehicle control	336	
	nuclear extract only	5301	
67	1 μ M	1483	77
67	0.1 μ M	2110	64
67	0.01 μ M	4084	25

SEQUENCE LISTING

[0164]

<110> Novartis AG

<120> Use of inhibitors of the activity or function of PI3K

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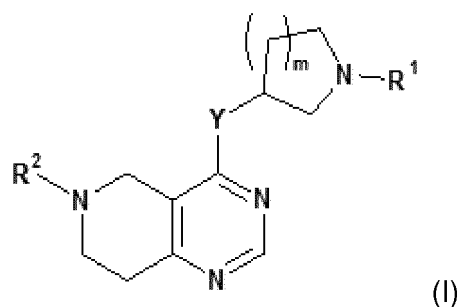
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Claims

- 50 1. A PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, for use in the treatment of immunopathology in a subject suffering from a disease or disorder selected from acute and cerebral malaria, via functional inhibition of TLR9 of the infected subject, wherein the PI3K inhibitor is selected from tetrahydro-pyrido-pyrimidine compounds of the formula (I) and/or tautomers and/or N-oxides and/or pharmaceutically acceptable salts thereof,
- 55



wherein

Y is selected from O or NR³;

R¹ is selected from phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, or

-C(O)-R⁴

wherein

R⁴ is selected from C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, C₁-C₈-alkoxy-C₁-C₈-alkyl, C₁-C₈-alkyl-sulfonyl-C₁-C₈-alkyl, heterocyclyl, heterocyclyl-oxy, heterocyclyl-C₁-C₈-alkyl, C₃-C₁₂-cycloalkyl, C₃-C₁₂-cycloalkyl-C₁-C₈-alkyl, heteroaryl, heteroaryl-oxy, heteroaryl-C₁-C₈-alkyl, hydroxy, C₁-C₈-alkoxy, amino, N-C₁-C₈-alkyl-amino or N,N-di-C₁-C₈-alkyl-amino, wherein 'C₁-C₈-alkyl' in N-C₁-C₈-alkyl-amino and N,N-di-C₁-C₈-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C₁-C₄-alkoxy;

wherein 'C₃-C₁₂-cycloalkyl' in C₃-C₁₂-cycloalkyl and C₃-C₁₂-cycloalkyl-C₁-C₈-alkyl may be unsubstituted or substituted by 1-5 substituents independently selected from oxo, halogen, C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkoxy-C₁-C₈-alkyl, amino, N-C₁-C₈-alkyl-amino, N,N-di-C₁-C₈-alkyl-amino, C₁-C₈-alkyl-carbonyl, halo-C₁-C₈-alkyl-carbonyl, hydroxy-C₁-C₈-alkyl-carbonyl or C₁-C₈-alkoxy-C₁-C₈-alkyl-carbonyl;

wherein 'heterocyclyl' is selected from oxiranyl, aziridinyl, oxetanyl, thiethanyl, acetitanyl, pyrrolidinyl, tetrahydrofuranlyl, tetrahydrothiophenyl, 2,3-dihydrofuranlyl, 2,5-dihydrofuranlyl, 2,3-dihydrothiophenyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, tetrahydropyranlyl, piperidinyl, tetrahydrothiopyranlyl, morpholinyl, thiomorpholinyl, piperazinyl, azepanyl, thiepanyl or oxepanyl; each of which is unsubstituted or substituted by 1-5 substituents independently selected from oxo, halogen, C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkoxy-C₁-C₈-alkyl, amino, N-C₁-C₈-alkyl-amino, N,N-di-C₁-C₈-alkyl-amino, C₁-C₈-alkyl-carbonyl, halo-C₁-C₈-alkyl-carbonyl, hydroxy-C₁-C₈-alkyl-carbonyl or C₁-C₈-alkoxy-C₁-C₈-alkyl-carbonyl;

wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

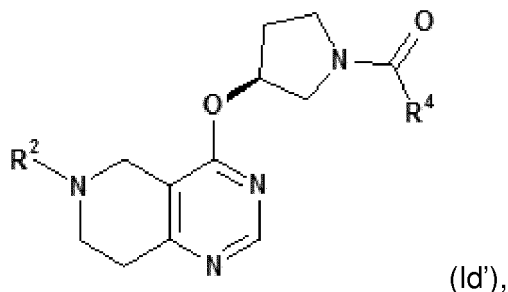
wherein 'heteroaryl' is selected from

furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl or 1,3,5-triazinyl; each of which is unsubstituted or substituted by 1-5 substituents independently selected from halogen, C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkoxy-C₁-C₈-alkyl, amino, N-C₁-C₈-alkyl-amino, N,N-di-C₁-C₈-alkyl-amino, C₁-C₈-alkyl-carbonyl, halo-C₁-C₈-alkyl-carbonyl, hydroxy-C₁-C₈-alkyl-carbonyl or C₁-C₈-alkoxy-C₁-C₈-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

R² is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl or isoquinolinyl, each of which is unsubstituted or substituted by 1-5 substituents independently selected from halogen, cyano, nitro, C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkoxy-C₁-C₈-alkyl, amino, N-C₁-C₈-alkyl-amino, N,N-di-C₁-C₈-alkyl-amino, C₁-C₈-alkyl-carbonyl, halo-C₁-C₈-alkyl-carbonyl, hydroxy-

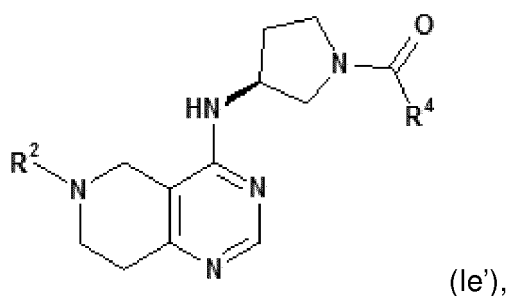
C₁-C₈-alkylcarbonyl or C₁-C₈-alkoxy-C₁-C₈-alkyl-carbonyl;
 R³ is selected from H, C₁-C₄-alkyl or halo-C₁-C₄-alkyl; and
 m is selected from 0 or 1.

2. A PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, for use according to claim 1 of the formula (Id')



and/or tautomers and/or N-oxides and/or pharmaceutically acceptable salts thereof.

3. A PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, for use according to claim 1 of the formula (Ie')



and/or tautomers and/or N-oxides and/or pharmaceutically acceptable salts thereof.

4. A PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, for use according to any one of claims 1 to 3, wherein
 R² is selected from naphthyl, pyridyl or pyrimidinyl; each of which is unsubstituted or substituted by 1-3 substituents independently selected from halogen, cyano, nitro, C₁-C₈-alkyl, halo-C₁-C₈-alkyl, hydroxy-C₁-C₈-alkyl, hydroxyl, C₁-C₈-alkoxy, C₁-C₈-alkoxy-C₁-C₈-alkyl, amino, N-C₁-C₈-alkyl-amino, N,N-di-C₁-C₈-alkyl-amino, C₁-C₈-alkyl-carbonyl, halo-C₁-C₈-alkyl-carbonyl, hydroxy-C₁-C₈-alkyl-carbonyl or C₁-C₈-alkoxy-C₁-C₈-alkyl-carbonyl.

5. A PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, for use according to any one of claims 1 to 4, wherein
 R¹, if present, is -C(O)-R⁴, wherein
 R⁴ is selected from heterocyclyl, C₄-C₈-cycloalkyl or heteroaryl;
 wherein 'C₃-C₁₂-cycloalkyl' may be unsubstituted or substituted by 1-3 substituents independently selected from fluoro, C₁-C₄-alkyl, hydroxyl, C₁-C₄-alkoxy;
 wherein 'heterocyclyl' is selected from pyrrolidinyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl or piperazinyl; each of which is unsubstituted or substituted by 1-3 substituents independently selected from oxo, halogen, C₁-C₄-alkyl, hydroxyl, C₁-C₄-alkyl-carbonyl;
 wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;
 wherein 'heteroaryl' is selected from
 furanyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, 1,3,4-oxadiazolyl, pyridyl, pyrazinyl; each of which is unsubstituted or substituted by 1-3 substituents independently selected from C₁-C₄-alkyl, hydroxyl;
 wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can

also optionally be oxidized to various oxidation states.

6. A PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, for use according to any one of claims 1 to 4, wherein

R¹, if present, is -C(O)-R⁴, and

R⁴ is selected from C₁-C₈-alkyl, C₁-C₈-alkoxy-C₁-C₈-alkyl, C₁-C₈-alkoxy or N,N-di-C₁-C₈-alkyl-amino, wherein 'C₁-C₈-alkyl' in N,N-di-C₁-C₈-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C₁-C₄-alkoxy.

7. A PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, for use according to claim 1, wherein the PI3K inhibitor is selected from the group consisting of

{{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;

{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;

{{(S)-3-[6-(2,4-Dimethoxy-pyrimidin-5-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;

{3-[6-(2,4-Dimethoxy-pyrimidin-5-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;

2-Methoxy-5-{4-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

2-Methoxy-5-{4-[1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

1-{(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-propan-1-one;

1-{3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-propan-1-one;

{{(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;

{3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;

2-Amino-5-{4-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

2-Amino-5-{4-[1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;

(S)-(3-(6-(5-Fluoro-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;

(3-(6-(5-Fluoro-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;

(S)-2-Methoxy-5-(4-(1-(2-methoxyacetyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;

2-Methoxy-5-(4-(1-(2-methoxyacetyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;

(S)-5-(4-(1-(Cyclopentanecarbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-methoxynicotinonitrile;

5-(4-(1-(Cyclopentanecarbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-methoxynicotinonitrile;

(2,4-Dimethyl-oxazol-5-yl)-{(S)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

(2,4-Dimethyl-oxazol-5-yl)-{3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

Furan-3-yl-{{(S)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

Furan-3-yl-{3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

Furan-3-yl-{{(S)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

Furan-3-yl-{3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-3H-imidazol-4-yl)-methanone;
 5 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-3H-imidazol-4-yl)-methanone;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2-methyl-oxazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2-methyl-oxazol-4-yl)-methanone;
 10 (3-Methoxy-cyclobutyl)-{(S)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 (3-Methoxy-cyclobutyl)-{3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 15 {{{S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-4-yl-methanone;
 ({3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-4-yl-methanone;
 1-(4-{{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-piperidin-1-yl)-ethanone;
 20 1-(4-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-piperidin-1-yl)-ethanone;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(4-methyl-oxazol-5-yl)-methanone;
 25 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(4-methyl-oxazol-5-yl)-methanone;
 5-{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-1H-pyridin-2-one;
 5-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-1H-pyridin-2-one;
 30 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone;
 35 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-4-yl-methanone;
 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-4-yl-methanone;
 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-5-yl-methanone;
 40 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-oxazol-5-yl-methanone;
 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2-methyl-oxazol-4-yl)-methanone;
 45 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2-methyl-oxazol-4-yl)-methanone;
 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2,2-dimethyl-tetrahydro-pyran-4-yl)-methanone;
 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2,2-dimethyl-tetrahydro-pyran-4-yl)-methanone;
 50 {(S)-3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2,4-dimethyl-oxazol-5-yl)-methanone;
 {3-[6-(5,6-Dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(2,4-dimethyl-oxazol-5-yl)-methanone;
 55 (4,4-Difluoro-cyclohexyl)-{(S)-3-[6-(5,6-dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 (4,4-Difluoro-cyclohexyl)-{3-[6-(5,6-dimethoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;

2-Methoxy-5-{4-[(S)-1-(2-tetrahydro-pyran-4-yl-acetyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 2-Methoxy-5-{4-[1-(2-tetrahydro-pyran-4-yl-acetyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 5-{4-[(S)-1-(2,4-Dimethyl-oxazole-5-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxy-nicotinonitrile;
 5-{4-[1-(2,4-Dimethyl-oxazole-5-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxy-nicotinonitrile;
 5-{4-[(S)-1-(2,2-Dimethyl-tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxy-nicotinonitrile;
 5-{4-[1-(2,2-Dimethyl-tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxy-nicotinonitrile;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(5-methyl-oxazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(5-methyl-oxazol-4-yl)-methanone;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-isoxazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-isoxazol-4-yl)-methanone;
 {(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-isoxazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(3-methyl-isoxazol-4-yl)-methanone;
 Isoxazol-3-yl-[(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl]-methanone;
 Isoxazol-3-yl-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 Isoxazol-5-yl-[(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl]-methanone;
 Isoxazol-5-yl-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 2-Methoxy-5-{4-[(S)-1-(thiazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 2-Methoxy-5-{4-[1-(thiazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 2-Methoxy-5-{4-[(S)-1-(1-methyl-1H-pyrazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 2-Methoxy-5-{4-[1-(1-methyl-1H-pyrazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 2-Methoxy-5-{4-[(S)-1-(1-methyl-1H-pyrazole-3-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 2-Methoxy-5-{4-[1-(1-methyl-1H-pyrazole-3-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile;
 (2,2-Dimethyl-tetrahydro-pyran-4-yl)-{(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 (2,2-Dimethyl-tetrahydro-pyran-4-yl)-{3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 (1,1-Dioxo-hexahydro-1 λ 6*-thiopyran-4-yl)-{(S)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 (1,1-Dioxo-hexahydro-1 λ 6*-thiopyran-4-yl)-{3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-methanone;
 (S)-(2,4-Dimethyloxazol-5-yl){3-[6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}methanone;

(2,4-Dimethyloxazol-5-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(thiazol-5-yl)methanone;
 5 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(thiazol-5-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-methyl-1H-pyrazol-5-yl)methanone;
 10 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-methyl-1H-pyrazol-5-yl)methanone;
 4-((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)pyrrolidin-2-one;
 4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)pyrrolidin-2-one;
 15 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyridin-3-yl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyridin-3-yl)methanone;
 (S)-(1H-Imidazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
 20 (1H-Imidazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
 5-((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)pyrrolidin-2-one;
 25 5-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)pyrrolidin-2-one;
 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyridin-4-yl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyridin-4-yl)methanone;
 30 (S)-(1,3-Dimethyl-1H-pyrazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
 (1,3-Dimethyl-1H-pyrazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
 35 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1H-pyrazol-4-yl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1H-pyrazol-4-yl)methanone;
 (S)-(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(5-methyl-1,3,4-oxadiazol-2-yl)methanone;
 40 (3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(5-methyl-1,3,4-oxadiazol-2-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyrazin-2-yl)methanone;
 45 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyrazin-2-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-methyl-1H-imidazol-4-yl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-methyl-1H-imidazol-4-yl)methanone;
 50 {(S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-pyrazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-pyrazol-4-yl)-methanone;
 55 {(S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-thiazol-4-yl-methanone;
 {3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-thiazol-4-yl-methanone;

{(S)-3-[6-(5-Chloro-6-methoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 {3-[6-(5-Chloro-6-methoxy-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 5 (S)-(3-(6-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (3-(6-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 10 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)azetidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 {(S)-3-[6-(2-Methoxy-pyrimidin-5-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 {3-[6-(2-Methoxy-pyrimidin-5-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 15 [(S)-3-(6-Quinolin-3-yl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 [3-(6-Quinolin-3-yl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone;
 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 20 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (S)-1-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-3,3-dimethylbutan-1-one;
 25 1-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-3,3-dimethylbutan-1-one;
 1-((S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-propan-1-one;
 1-{3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-propan-1-one;
 30 2-Methoxy-5-[4-((S)-1-propionyl-pyrrolidin-3-yloxy)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-nicotinonitrile;
 2-Methoxy-5-[4-(1-propionyl-pyrrolidin-3-yloxy)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-nicotinonitrile;
 (S)-6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-4-(1-(pyridin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;
 35 6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-4-(1-(pyridin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;
 (S)-6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-4-(1-(pyrimidin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;
 6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-4-(1-(pyrimidin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;
 40 (S)-1-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)propan-1-one;
 1-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)propan-1-one;
 45 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (S)-2-Methoxy-5-(4-(1-(tetrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-ylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;
 50 2-Methoxy-5-(4-(1-(tetrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-ylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;
 (S)-1-(4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-carbonyl)piperidin-1-yl)ethanone;
 55 1-(4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-carbonyl)piperidin-1-yl)ethanone;
 (2,2-Dimethyltetrahydro-2H-pyran-4-yl)((S)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;

(2,2-Dimethyltetrahydro-2H-pyran-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)methanone;
 5 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)methanone;
 ((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)((1s,4R)-4-methoxycyclohexyl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)((1s,4R)-4-methoxycyclohexyl)methanone;
 10 ((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)((1r,4S)-4-methoxycyclohexyl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)((1r,4S)-4-methoxycyclohexyl)methanone;
 15 ((1s,4R)-4-Hydroxycyclohexyl)((S)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 ((1s,4R)-4-Hydroxycyclohexyl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 ((1r,4S)-4-Hydroxycyclohexyl)((S)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 20 ((1r,4S)-4-Hydroxycyclohexyl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(1-methyl-1H-imidazol-4-yl)methanone;
 25 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(1-methyl-1H-imidazol-4-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)methanone;
 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)methanone;
 30 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-4-yl)methanone;
 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-4-yl)methanone;
 35 (2,2-Dimethyltetrahydro-2H-pyran-4-yl)((S)-3-(6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 (2,2-Dimethyltetrahydro-2H-pyran-4-yl)(3-(6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanone;
 (S)-1-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)propan-1-one;
 40 1-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)propan-1-one;
 (S)-(3-(6-(5-Chloro-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 45 (3-(6-(5-Chloro-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone;
 50 (Tetrahydro-pyran-4-yl)-((S)-3-(6-(5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)-methanone;
 (Tetrahydro-pyran-4-yl)-3-(6-(5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)-methanone;
 55 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(4-methylpiperazin-1-yl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(4-methylpiperazin-1-yl)methanone;

(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(morpholino)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(morpholino)methanone;
 5 (S)-(4-Hydroxypiperidin-1-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
 4-Hydroxypiperidin-1-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanone;
 (S)-N-(2-Hydroxyethyl)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)-N-methylpyrrolidine-1-carboxamide;
 10 N-(2-Hydroxyethyl)-3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)-N-methylpyrrolidine-1-carboxamide;
 (S)-1-(4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)piperazin-1-yl)ethanone;
 15 1-(4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)piperazin-1-yl)ethanone;
 (S)-2-Methoxy-5-(4-(1-(morpholine-4-carbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;
 2-Methoxy-5-(4-(1-(morpholine-4-carbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile;
 20 (S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(oxazol-4-yl)methanone;
 (3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(oxazol-4-yl)methanone;
 25 1-(4-((S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl)-piperidin-1-yl)-ethanone;
 1-(4-{3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-piperidin-1-yl)-ethanone;
 30 {(S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(3-methyl-3H-imidazol-4-yl)-methanone;
 {3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(3-methyl-3H-imidazol-4-yl)-methanone;
 {(S)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-oxazol-5-yl-methanone;
 35 {3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-oxazol-5-yl-methanone;
 {(S)-3-[6-(6-Methoxy-pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone; and
 {3-[6-(6-Methoxy-pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone.

8. A PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, for use according to anyone of claims 1 to 7 in form of a salt selected from

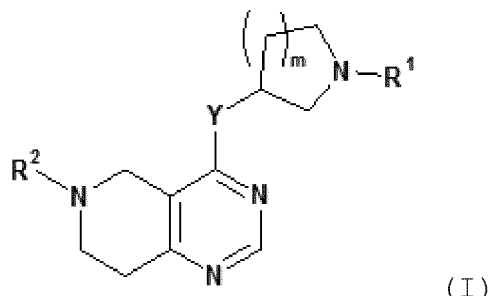
- a) citrate, fumarate or napadisylate; or
 b) phosphate, hydrochloride or hippurate.

9. A pharmaceutical composition comprising a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, or pharmaceutically acceptable salts or solvates thereof, wherein the PI3K inhibitor is as defined in any of claims 1 to 8, for use in the treatment of immunopathology in a subject suffering from a disease or disorder selected from acute and cerebral malaria, via functional inhibition of TLR9 of the infected subject.

10. A combination comprising a PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, or pharmaceutically acceptable salts or solvates thereof, wherein the PI3K inhibitor is as defined in any of claims 1 to 8, for use in the treatment of immunopathology in a subject suffering from a disease or disorder selected from acute and cerebral malaria, via functional inhibition of TLR9 of the infected subject, and one or more additional active ingredients.

Patentansprüche

1. PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, zur Verwendung bei der Behandlung von Immunpathologie bei einem an einer Krankheit bzw. Störung ausgewählt aus akuter und zerebraler Malaria leidenden Subjekt, durch funktionale Inhibierung von TLR9 des infizierten Subjekts, wobei der PI3K-Inhibitor aus Tetrahydropyridopyrimidinverbindungen der Formel (I) und/oder Tautomeren und/oder N-Oxiden und/oder pharmazeutisch unbedenklichen Salzen davon ausgewählt ist,



wobei

Y aus O und NR³ ausgewählt ist,

R¹ aus Phenyl, Pyridyl, Pyrimidinyl, Pyrazinyl, Pyridazinyl, 1,2,3-Triazinyl, 1,2,4-Triazinyl, 1,3,5-Triazinyl und -C(O)-R⁴ ausgewählt ist,

wobei

R⁴ aus C₁-C₈-Alkyl, Halogen-C₁-C₈-alkyl, Hydroxy-C₁-C₈-alkyl, C₁-C₈-Alkoxy-C₁-C₈-alkyl, C₁-C₈-Alkyl-sulfonyl-C₁-C₈-alkyl, Heterocyclyl, Heterocycloxy, Heterocyclyl-C₁-C₈-alkyl, C₃-C₁₂-Cycloalkyl, C₃-C₁₂-Cycloalkyl-C₁-C₈-alkyl, Heteroaryl, Heteroaryloxy, Heteroaryl-C₁-C₈-alkyl, Hydroxy, C₁-C₈-Alkoxy, Amino, N-C₁-C₈-Alkylamino und N,N-Di-C₁-C₈-alkylamino ausgewählt ist,

wobei 'C₁-C₈-Alkyl' in N-C₁-C₈-Alkylamino und N,N-Di-C₁-C₈-alkylamino unsubstituiert oder durch Halogen, Hydroxy oder C₁-C₄-Alkoxy substituiert sein kann,

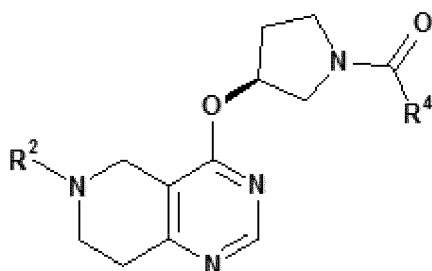
wobei 'C₃-C₁₂-Cycloalkyl' in C₃-C₁₂-Cycloalkyl und C₃-C₁₂-Cycloalkyl-C₁-C₈-alkyl unsubstituiert oder durch 1-5 unabhängig voneinander aus Oxo, Halogen, C₁-C₈-Alkyl, Halogen-C₁-C₈-alkyl, Hydroxy-C₁-C₈-alkyl, Hydroxy, C₁-C₈-Alkoxy, C₁-C₈-Alkoxy-C₁-C₈-alkyl, Amino, N-C₁-C₈-Alkylamino, N,N-Di-C₁-C₈-alkylamino, C₁-C₈-Alkylcarbonyl, Halogen-C₁-C₈-alkylcarbonyl, Hydroxy-C₁-C₈-alkylcarbonyl und C₁-C₈-Alkoxy-C₁-C₈-alkylcarbonyl ausgewählte Substituenten substituiert sein kann,

wobei 'Heterocyclyl' aus Oxiranyl, Aziridinyl, Oxetanyl, Thiethanyl, Acetidinyl, Pyrrolidinyl, Tetrahydrofuran-yl, Tetrahydrothiophenyl, 2,3-Dihydrofuran-yl, 2,5-Dihydrofuran-yl, 2,3-Dihydrothiophenyl, 1-Pyrrolinyl, 2-Pyrrolinyl, 3-Pyrrolinyl, Tetrahydropyran-yl, Piperidinyl, Tetrahydrothiopyran-yl, Morpholinyl, Thiomorpholin-yl, Piperazinyl, Azepanyl, Thiepanyl und Oxepanyl ausgewählt ist, die jeweils unsubstituiert oder durch 1-5 unabhängig voneinander aus Oxo, Halogen, C₁-C₈-Alkyl, Halogen-C₁-C₈-alkyl, Hydroxy-C₁-C₈-alkyl, Hydroxy, C₁-C₈-Alkoxy, C₁-C₈-Alkoxy-C₁-C₈-alkyl, Amino, N-C₁-C₈-Alkylamino, N,N-Di-C₁-C₈-alkylamino, C₁-C₈-Alkylcarbonyl, Halogen-C₁-C₈-alkylcarbonyl, Hydroxy-C₁-C₈-alkylcarbonyl und C₁-C₈-Alkoxy-C₁-C₈-alkylcarbonyl ausgewählte Substituenten substituiert sind,

wobei 'Heterocyclyl' an ein Heteroatom oder ein Kohlenstoffatom gebunden sein kann und wobei die N- und/oder S-Heteroatome außerdem gegebenenfalls zu verschiedenen Oxidationsstufen oxidiert sein können, wobei 'Heteroaryl' aus Furanyl, Thiophenyl, Pyrrolyl, Imidazolyl, Pyrazolyl, Thiazolyl, Isothiazolyl, Oxazolyl, Isoxazolyl, 1,2,5-Oxadiazolyl, 1,2,4-Oxadiazolyl, 1,2,3-Oxadiazolyl, 1,3,4-Oxadiazolyl, 1,2,5-Thiadiazolyl, 1,2,4-Thiadiazolyl, 1,2,3-Thiadiazolyl, 1,3,4-Thiadiazolyl, 1,2,3-Triazolyl, 1,2,4-Triazolyl, 1,2,5-Triazolyl, Pyridyl, Pyrimidinyl, Pyrazinyl, Pyridazinyl, 1,2,3-Triazinyl, 1,2,4-Triazinyl und 1,3,5-Triazinyl ausgewählt ist, die jeweils unsubstituiert oder durch 1-5 unabhängig voneinander aus Halogen, C₁-C₈-Alkyl, Halogen-C₁-C₈-alkyl, Hydroxy-C₁-C₈-alkyl, Hydroxy, C₁-C₈-Alkoxy, C₁-C₈-Alkoxy-C₁-C₈-alkyl, Amino, N-C₁-C₈-Alkylamino, N,N-Di-C₁-C₈-alkylamino, C₁-C₈-Alkylcarbonyl, Halogen-C₁-C₈-alkylcarbonyl, Hydroxy-C₁-C₈-alkylcarbonyl und C₁-C₈-Alkoxy-C₁-C₈-alkylcarbonyl ausgewählte Substituenten substituiert sind, wobei 'Heteroaryl' an ein Heteroatom oder ein Kohlenstoffatom gebunden sein kann und wobei die N- und/oder S-Heteroatome außerdem gegebenenfalls zu verschiedenen Oxidationsstufen oxidiert sein können,

R² aus Phenyl, Naphthyl, Pyridyl, Pyrimidinyl, Pyrazinyl, Pyridazinyl, Chinolinyll und Isochinolinyll ausgewählt ist, die jeweils unsubstituiert oder durch 1-5 unabhängig voneinander aus Halogen, Cyano, Nitro, C₁-C₈-Alkyl, Halogen-C₁-C₈-alkyl, Hydroxy-C₁-C₈-alkyl, Hydroxy, C₁-C₈-Alkoxy, C₁-C₈-Alkoxy-C₁-C₈-alkyl, Amino, N-C₁-C₈-Alkylamino, N,N-Di-C₁-C₈-alkylamino, C₁-C₈-Alkylcarbonyl, Halogen-C₁-C₈-alkylcarbonyl, Hydroxy-C₁-C₈-alkylcarbonyl und C₁-C₈-Alkoxy-C₁-C₈-alkylcarbonyl ausgewählte Substituenten substituiert sind, R³ aus H, C₁-C₄-Alkyl und Halogen-C₁-C₄-alkyl ausgewählt ist und m aus 0 und 1 ausgewählt ist.

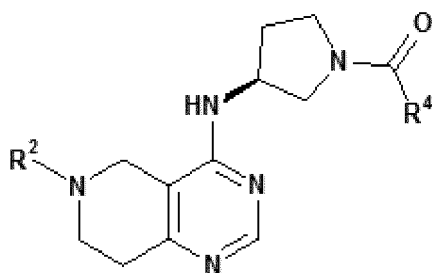
2. PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, zur Verwendung nach Anspruch 1, mit der Formel (Id')



(Id'),

und/oder Tautomere und/oder N-Oxide und/oder pharmazeutisch unbedenkliche Salze davon.

3. PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, zur Verwendung nach Anspruch 1, mit der Formel (Ie')



(Ie'),

und/oder Tautomere und/oder N-Oxide und/oder pharmazeutisch unbedenkliche Salze davon.

4. PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, zur Verwendung nach einem der Ansprüche 1 bis 3, wobei R² aus Naphthyl, Pyridyl und Pyrimidinyl ausgewählt ist, die jeweils unsubstituiert oder durch 1-3 unabhängig voneinander aus Halogen, Cyano, Nitro, C₁-C₈-Alkyl, Halogen-C₁-C₈-alkyl, Hydroxy-C₁-C₈-alkyl, Hydroxy, C₁-C₈-Alkoxy, C₁-C₈-Alkoxy-C₁-C₈-alkyl, Amino, N-C₁-C₈-Alkylamino, N,N-Di-C₁-C₈-alkylamino, C₁-C₈-Alkylcarbonyl, Halogen-C₁-C₈-alkylcarbonyl, Hydroxy-C₁-C₈-alkylcarbonyl und C₁-C₈-Alkoxy-C₁-C₈-alkylcarbonyl ausgewählte Substituenten substituiert sind.

5. PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, zur Verwendung nach einem der Ansprüche 1 bis 4, wobei R¹, falls vorhanden, für -C(O)-R⁴ steht, wobei R⁴ aus Heterocyclyl, C₄-C₈-Cycloalkyl und Heteroaryl ausgewählt ist, wobei 'C₃-C₁₂-Cycloalkyl' unsubstituiert oder durch 1-3 unabhängig voneinander aus Fluor, C₁-C₄-Alkyl, Hydroxy und C₁-C₄-Alkoxy ausgewählte Substituenten substituiert sein kann, wobei 'Heterocyclyl' aus Pyrrolidinyl, Tetrahydropyranyl, Piperidinyl, Tetrahydrothiopyranyl, Morpholinyl und Piperazinyl ausgewählt ist, die jeweils unsubstituiert oder durch 1-3 unabhängig voneinander aus Oxo, Halogen, C₁-C₄-Alkyl, Hydroxy und C₁-C₄-Alkylcarbonyl ausgewählte Substituenten substituiert sind, wobei 'Heterocyclyl' an ein Heteroatom oder ein Kohlenstoffatom gebunden sein kann und wobei die N- und/oder S-Heteroatome außerdem gegebenenfalls zu verschiedenen Oxidationsstufen oxidiert sein können, wobei 'Heteroaryl' aus Furanyl, Imidazolyl, Pyrazolyl, Thiazolyl, Oxazolyl, Isoxazolyl, 1,3,4-Oxadiazolyl, Pyridyl und Pyrazinyl

ausgewählt ist, die jeweils unsubstituiert oder durch 1-3 unabhängig voneinander aus C₁-C₄-Alkyl und Hydroxy ausgewählte Substituenten substituiert sind,
wobei 'Heteroaryl' an ein Heteroatom oder ein Kohlenstoffatom gebunden sein kann und wobei die N- und/oder S-Heteroatome außerdem gegebenenfalls zu verschiedenen Oxidationsstufen oxidiert sein können.

6. PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, zur Verwendung nach einem der Ansprüche 1 bis 4, wobei
R¹, falls vorhanden, für -C(O)-R⁴ steht und
R⁴ aus C₁-C₈-Alkyl, C₁-C₈-Alkoxy-C₁-C₈-alkyl, C₁-C₈-Alkoxy und N,N-Di-C₁-C₈-alkylamino ausgewählt ist, wobei 'C₁-C₈-Alkyl' in N,N-Di-C₁-C₈-alkylamino unsubstituiert oder durch Halogen, Hydroxy oder C₁-C₄-Alkoxy substituiert sein kann.

7. PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, zur Verwendung nach Anspruch 1, wobei der PI3K-Inhibitor ausgewählt ist aus der Gruppe bestehend aus
{ (S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydropyran-4-yl)methanon,
{3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydropyran-4-yl)methanon,
{ (S)-3-[6-(4-Dimethoxypyrimidin-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydropyran-4-yl)methanon,
{3-[6-(2,4-Dimethoxypyrimidin-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydropyran-4-yl)methanon,
2-Methoxy-5-[4-[(S)-1-(tetrahydropyran-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]nicotinsäurenitril,
2-Methoxy-5-[4-[1-(tetrahydropyran-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]nicotinsäurenitril,
1-[(S)-3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl]propan-1-on,
1-{3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}propan-1-on,
{(S)-3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydropyran-4-yl)methanon,
{3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydropyran-4-yl)methanon,
2-Amino-5-[4-[(S)-1-(tetrahydropyran-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]nicotinsäurenitril,
2-Amino-5-[4-[1-(tetrahydropyran-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]nicotinsäurenitril,
(S)-(3-(6-(5-Fluor-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl) (tetrahydro-2H-pyran-4-yl)methanon,
(3-(6-(5-Fluor-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl) (tetrahydro-2H-pyran-4-yl)methanon,
(S)-2-Methoxy-5-(4-(1-(2-methoxyacetyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinsäurenitril,
2-Methoxy-5-(4-(1-(2-methoxyacetyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinsäurenitril,
(S)-5-(4-(1-(Cyclopentancarbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-methoxynicotinsäurenitril,
5-(4-(1-(Cyclopentancarbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-methoxynicotinsäurenitril,
(2,4-Dimethyloxazol-5-yl)-[(S)-3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl]methanon,
(2,4-Dimethyloxazol-5-yl)-{3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}methanon,
Furan-3-yl-{ (S)-3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}methanon,
Furan-3-yl-{3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}methanon,
Furan-3-yl-{ (S)-3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-

1-yl}methanon,

Furan-3-yl-{3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}methanon,

{{(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-methyl-3H-imidazol-4-yl)methanon,

{3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-methyl-3H-imidazol-4-yl)methanon,

{{(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2-methyloxazol-4-yl)methanon,

{3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2-methyloxazol-4-yl)methanon,

(3-Methoxycyclobutyl)-{(S)-3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}methanon,

(3-Methoxycyclobutyl)-{3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}methanon,

{{(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-4-ylmethanon,

{{3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-4-ylmethanon,

1-(4-{{(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-carbonyl}piperidin-1-yl)ethanon,

1-(4-{3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-carbonyl}piperidin-1-yl)ethanon,

{{(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(4-methyloxazol-5-yl)methanon,

{3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(4-methyloxazol-5-yl)methanon,

5-{{(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-carbonyl}-1H-pyridin-2-on,

5-{3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-carbonyl}-1H-pyridin-2-on,

{{(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)methanon,

{3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)methanon,

{{(S)-3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-4-ylmethanon,

{3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-4-ylmethanon,

{{(S)-3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-5-ylmethanon,

{3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-5-ylmethanon,

{{(S)-3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2-methyloxazol-4-yl)methanon,

{3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2-methyloxazol-4-yl)methanon,

{{(S)-3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2,2-dimethyltetrahydropyran-4-yl)methanon,

{3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2,2-dimethyltetrahydropyran-4-yl)methanon,

{{(S)-3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2,4-dimethyloxazol-5-yl)methanon,

{3-[6-(5,6-Dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2,4-dimethyloxazol-5-yl)methanon,

(4,4-Difluorocyclohexyl)-{(S)-3-[6-(5,6-dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}methanon,

(4,4-Difluorocyclohexyl)-{3-[6-(5,6-dimethoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}methanon,

din-1-yl)methanon,
 2-Methoxy-5-{4-[(S)-1-(2-tetrahydropyran-4-yl-acetyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinsäurenitril,
 2-Methoxy-5-{4-[1-(2-tetrahydropyran-4-yl-acetyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinsäurenitril,
 5-{4-[(S)-1-(2,4-Dimethyloxazol-5-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxynicotinsäurenitril,
 5-{4-[1-(2,4-Dimethyloxazol-5-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxynicotinsäurenitril,
 5-{4-[(S)-1-(2,2-Dimethyltetrahydropyran-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxynicotinsäurenitril,
 5-{4-[1-(2,2-Dimethyltetrahydropyran-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-methoxynicotinsäurenitril,
 {(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(5-methylloxazol-4-yl)methanon,
 {3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(5-methylloxazol-4-yl)methanon,
 {(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(5-methylisoxazol-4-yl)methanon,
 {3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(5-methylisoxazol-4-yl)methanon,
 {(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-methylisoxazol-4-yl)methanon,
 {3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-methylisoxazol-4-yl)methanon,
 {(S)-3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-methylisoxazol-4-yl)methanon,
 {3-[6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-methylisoxazol-4-yl)methanon,
 Isoxazol-3-yl-[(S)-3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)methanon,
 Isoxazol-3-yl-{3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)methanon,
 Isoxazol-5-yl-[(S)-3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)methanon,
 Isoxazol-5-yl-{3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)methanon,
 2-Methoxy-5-{4-[(S)-1-(thiazol-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinsäurenitril,
 2-Methoxy-5-{4-[1-(thiazol-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinsäurenitril,
 2-Methoxy-5-{4-[(S)-1-(1-methyl-1H-pyrazol-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinsäurenitril,
 2-Methoxy-5-{4-[1-(1-methyl-1H-pyrazol-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinsäurenitril,
 2-Methoxy-5-{4-[(S)-1-(1-methyl-1H-pyrazol-3-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinsäurenitril,
 2-Methoxy-5-{4-[1-(1-methyl-1H-pyrazol-3-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinsäurenitril,
 (2,2-Dimethyltetrahydropyran-4-yl)-{(S)-3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)methanon,
 (2,2-Dimethyltetrahydropyran-4-yl)-{3-[6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)methanon,
 (1,1-Dioxohexahydro-1λ⁶-thiopyran-4-yl)-{(S)-3-[6-(6-methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)methanon,
 (1,1-Dioxohexahydro-1λ⁶-thiopyran-4-yl)-{3-[6-(6-methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)methanon,
 (S)-(2,4-Dimethyloxazol-5-yl) (3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimi-

din-4-yloxy)pyrrolidin-1-yl)methanon,
d(2,4-Dimethoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-
4-yloxy)pyrrolidin-1-yl)methanon,
(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
yl)(thiazol-5-yl)methanon,
(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(thia-
zol-5-yl)methanon,
(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
yl)(1-methyl-1H-pyrazol-5-yl)methanon,
(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-
methyl-1H-pyrazol-5-yl)methanon,
4-((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
carbonyl)pyrrolidin-2-on,
4-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-car-
bonyl)pyrrolidin-2-on,
(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
yl)(pyridin-3-yl)methanon,
(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(pyri-
din-3-yl)methanon,
(S)-(1H-imidazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-
yloxy)pyrrolidin-1-yl)methanon,
(1H-imidazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylo-
xy)pyrrolidin-1-yl)methanon,
5-((S)-3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
carbonyl)pyrrolidin-2-on,
5-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-car-
bonyl)pyrrolidin-2-on,
(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
yl)(pyridin-4-yl)methanon,
(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(py-
ridin-4-yl)methanon,
(S)-(1,3-Dimethyl-1H-pyrazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-
d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanon,
(1,3-Dimethyl-1H-pyrazol-4-yl)(3-(6-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyri-
midin-4-yloxy)pyrrolidin-1-yl)methanon,
(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
yl)(1H-pyrazol-4-yl)methanon,
(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
yl)(1H-pyrazol-4-yl)methanon,
(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
yl)(5-methyl-1,3,4-oxadiazol-2-yl)methanon,
(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(5-
methyl-1,3,4-oxadiazol-2-yl)methanon,
(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
yl)(pyrazin-2-yl)methanon,
(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(py-
razin-2-yl)methanon,
(S)-(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
yl)(1-methyl-1H-imidazol-4-yl)methanon,
(3-(6-(6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(1-
methyl-1H-imidazol-4-yl)methanon,
{ (S)-3-[6-(6-Methoxy-5-trifluoromethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-
yl}-(1-methyl-1H-pyrazol-4-yl)methanon,
{3-[6-(6-Methoxy-5-trifluoromethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-{1-
methyl-1H-pyrazol-4-yl)methanon,
{ (S)-3-[6-(6-Methoxy-5-trifluoromethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-
yl}thiazol-4-ylmethanon,
{3-[6-(6-Methoxy-5-trifluoromethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}thia-

zol-4-ylmethanon,
 {(S)-3-[6-(5-Chlor-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydro-
 pyran-4-yl)methanon,
 {3-[6-(5-Chlor-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydro-
 5 pyran-4-yl)methanon,
 (S)-(3-(6-(6-Amino-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
 yl)(tetrahydro-2H-pyran-4-yl)methanon,
 (3-(6-(6-Amino-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl) (tetra-
 hydro-2H-pyran-4-yl)methanon,
 10 (3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)azetidin-1-yl)(te-
 trahydro-2H-pyran-4-yl)methanon,
 {(S)-3-[6-(2-Methoxypyrimidin-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydro-
 pyran-4-yl)methanon,
 {3-[6-(2-Methoxypyrimidin-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tetrahydro-
 15 4-yl)methanon,
 [(S)-3-(6-Chinolin-3-yl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl]-(tetrahydro-
 pyran-4-yl)methanon,
 [3-(6-Chinolin-3-yl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl]-(tetrahydro-
 20 pyran-4-yl)methanon,
 (S)-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
 yl)(tetrahydro-2H-pyran-4-yl)methanon,
 (3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(te-
 trahydro-2H-pyran-4-yl)methanon,
 25 (S)-1-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-
 yl)-3,3-dimethylbutan-1-on,
 1-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-
 3,3-dimethylbutan-1-on,
 1-((S)-3-[6-(6-Methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-
 yl)propan-1-on,
 30 1-{3-[6-(6-Methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}pro-
 pan-1-on,
 2-Methoxy-5-[4-((S)-1-propionylpyrrolidin-3-yloxy)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]nicotinsäurenitril,
 2-Methoxy-5-[4-(1-propionylpyrrolidin-3-yloxy)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]nicotinsäurenitril,
 35 (S)-6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-4-(1-(pyridin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-
 d]pyrimidin,
 6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-4-(1-(pyridin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-d]py-
 rimidin,
 (S)-6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-4-(1-(pyrimidin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyri-
 do[4,3-d]pyrimidin,
 40 6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-4-(1-(pyrimidin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tetrahydropyrido[4,3-
 d]pyrimidin,
 (S)-1-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-
 1-yl)propan-1-on,
 1-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 45 yl)propan-1-on,
 (S)-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 yl)(tetrahydro-2H-pyran-4-yl)methanon,
 (3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 yl)(tetrahydro-2H-pyran-4-yl)methanon,
 50 (S)-2-Methoxy-5-(4-(1-(tetrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-ylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-
 6(5H)-yl)nicotinsäurenitril,
 2-Methoxy-5-(4-(1-(tetrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-ylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-
 6(5H)-yl)nicotinsäurenitril,
 (S)-1-(4-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrroli-
 55 din-1-carbonyl)piperidin-1-yl)ethanon,
 1-(4-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-
 1-carbonyl)piperidin-1-yl)ethanon,
 (2,2-Dimethyltetrahydro-2H-pyran-4-yl) ((S)-3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyri-

do[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanon,
 (2,2-Dimethyltetrahydro-2H-pyran-4-yl) (3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyri-
 do[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanon,
 5 -(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 yl)(oxazol-5-yl)methanon,
 (3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 yl)(oxazol-5-yl)methanon,
 ((S)-3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 yl)((1s,4R)-4-methoxycyclohexyl)methanon,
 10 (3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 yl)((1s,4R)-4-methoxycyclohexyl)methanon,
 ((S)-3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 yl)((1r,4S)-4-methoxycyclohexyl)methanon,
 (3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 15 yl)((1r,4S)-4-methoxycyclohexyl)methanon,
 ((1s,4R)-4-Hydroxycyclohexyl)((S)-3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-
 d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanon,
 ((1s,4R)-4-Hydroxycyclohexyl)(3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyri-
 midin-4-ylamino)pyrrolidin-1-yl)methanon,
 20 ((1r,4S)-4-Hydroxycyclohexyl)((S)-3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]py-
 rimidin-4-ylamino)pyrrolidin-1-yl)methanon,
 ((1r,4S)-4-Hydroxycyclohexyl)(3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyri-
 midin-4-ylamino)pyrrolidin-1-yl)methanon,
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(1-
 25 methyl-1H-imidazol-4-yl)methanon,
 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(1-me-
 thyl-1H-imidazol-4-yl)methanon,
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxa-
 zol-5-yl)methanon,
 30 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-
 5-yl)methanon,
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxa-
 zol-4-yl)methanon,
 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-
 35 4-yl)methanon,
 (2,2-Dimethyltetrahydro-2H-pyran-4-yl) ((S)-3-(6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-
 d]pyrimidin-4-ylamino)pyrrolidin-1-yl)methanon,
 (2,2-Dimethyltetrahydro-2H-pyran-4-yl) (3-(6-(6-methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyri-
 midin-4-ylamino)pyrrolidin-1-yl)methanon,
 40 (S)-1-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-
 yl)propan-1-on,
 1-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)pro-
 pan-1-on,
 (S)-(3-(6-(5-Chlor-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetra-
 45 hydro-2H-pyran-4-yl)methanon,
 (3-(6-(5-Chlor-6-methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl) (tetrahy-
 dro-2H-pyran-4-yl)methanon,
 (S)-(3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(te-
 trahydro-2H-pyran-4-yl)methanon,
 50 (3-(6-(6-Methoxy-5-methylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tetrahy-
 dro-2H-pyran-4-yl)methanon,
 (Tetrahydropyran-4-yl)-{(S)-3-(6-(5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylami-
 no)pyrrolidin-1-yl)methanon,
 (Tetrahydropyran-4-yl)-{3-(6-(5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyr-
 55 rolidin-1-yl)methanon,
 -(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(4-
 methylpiperazin-1-yl)methanon,
 (3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(4-

methylpiperazin-1-yl)methanon,

(S)-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(morpholino)methanon,

(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(morpholino)methanon,

(S)-(4-Hydroxypiperidin-1-yl)(3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanon,

4-Hydroxypiperidin-1-yl)(3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)methanon,

(S)-N-(2-Hydroxyethyl)-3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)-N-methylpyrrolidin-1-carbonsäureamid,

N-(2-Hydroxyethyl)-3-(6-(6-methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)-N-methylpyrrolidin-1-carbonsäureamid,

(S)-1-(4-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-carbonyl)piperazin-1-yl)ethanon,

1-(4-(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-carbonyl)piperazin-1-yl)ethanon,

(S)-2-Methoxy-5-(4-(1-(morpholin-4-carbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinsäurenitril,

2-Methoxy-5-(4-(1-(morpholin-4-carbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinsäurenitril,

-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(oxazol-4-yl)methanon,

(3-(6-(6-Methoxy-5-(trifluormethyl)pyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)(oxazol-4-yl)methanon,

1-(4-((S)-3-[6-(6-Methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-carbonyl)piperidin-1-yl)ethanon,

1-(4-{3-[6-(6-Methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-carbonyl)piperidin-1-yl)ethanon,

{{(S)-3-[6-(6-Methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(3-methyl-3H-imidazol-4-yl)methanon,

{3-[6-(6-Methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(3-methyl-3H-imidazol-4-yl)methanon,

{{(S)-3-[6-(6-Methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-5-yl)methanon,

{3-[6-(6-Methoxy-5-trifluormethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-5-yl)methanon,

{{(S)-3-[6-(6-Methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tetrahydropyran-4-yl)methanon und

{3-[6-(6-Methoxypyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tetrahydropyran-4-yl)methanon.

8. PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, zur Verwendung nach einem der Ansprüche 1 bis 7, in Form eines Salzes ausgewählt aus

a) Citrat, Fumarat und Napadisylat oder

b) Phosphat, Hydrochlorid und Hippurat.

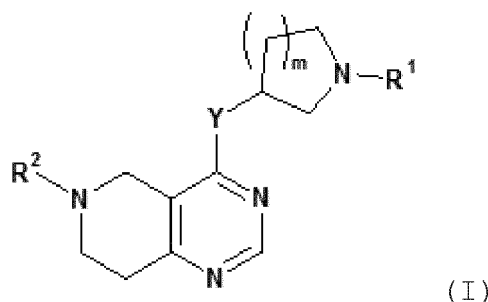
9. Pharmazeutische Zusammensetzung, umfassend einen PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, oder pharmazeutisch unbedenkliche Salze oder Solvate davon, wobei der PI3K-Inhibitor wie in einem der Ansprüche 1 bis 8 definiert ist, zur Verwendung bei der Behandlung von Immunpathologie in einem an einer Krankheit bzw. Störung ausgewählt aus akuter und zerebraler Malaria leidenden Subjekt, durch funktionelle Inhibierung von TLR9 des infizierten Subjekts.

10. Kombination, umfassend einen PI3K-Inhibitor, wobei der Inhibitor eine inhibierende Wirkung auf die PI3K-Isoform delta hat, oder pharmazeutisch unbedenkliche Salze oder Solvate davon, wobei der PI3K-Inhibitor wie in einem der Ansprüche 1 bis 8 definiert ist, zur Verwendung bei der Behandlung von Immunpathologie in einem an einer Krankheit bzw. Störung ausgewählt aus akuter und zerebraler Malaria leidenden Subjekt, durch funktionelle Inhibierung von

TLR9 des infizierten Subjekts, und einen oder mehrere zusätzliche Wirkstoffe.

Revendications

1. Inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, pour une utilisation dans le traitement d'une immunopathologie chez un sujet souffrant d'une maladie ou d'un trouble choisi(e) parmi le paludisme aigu et cérébral, via l'inhibition fonctionnelle de TLR9 du sujet infecté, où l'inhibiteur de PI3K est choisi parmi les composés de tétrahydropyridopyrimidine de formule (I), et/ou des tautomères et/ou N-oxydes et/ou sels pharmaceutiquement acceptables de celui-ci,



où

Y est choisi parmi O ou NR³ ;

R¹ est choisi parmi phényle, pyridyle, pyrimidinyle, pyrazinyle, pyridazinyle, 1,2,3-triazinyle, 1,2,4-triazinyle, 1,3,5-triazinyle,

ou

-C(O)-R⁴

où

R⁴ est choisi parmi C₁-C₈-alkyle, halogéno-C₁-C₈-alkyle, hydroxy-C₁-C₈-alkyle, C₁-C₈-alcoxy-C₁-C₈-alkyle, C₁-C₈-alkylsulfonyl-C₁-C₈-alkyle, hétérocyclyle, hétérocyclyloxy, hétérocyclyl-C₁-C₈-alkyle, C₃-C₁₂-cycloalkyle, C₃-C₁₂-cycloalkyl-C₁-C₈-alkyle, hétéroaryle, hétéroaryloxy, hétéroaryl-C₁-C₈-alkyle, hydroxy, C₁-C₈-alcoxy, amino, N-C₁-C₈-alkylamino ou N,N-di-C₁-C₈-alkylamino,

où « C₁-C₈-alkyle » dans N-C₁-C₈-alkylamino et N,N-di-C₁-C₈-alkylamino peut être non substitué ou substitué par halogène, hydroxy ou C₁-C₄-alcoxy ; où « C₃-C₁₂-cycloalkyle » dans C₃-C₁₂-cycloalkyle et C₃-C₁₂-cycloalkyl-C₁-C₈-alkyle peut être non substitué ou substitué par 1-5 substituants choisis indépendamment parmi oxo, halogène, C₁-C₈-alkyle, halogéno-C₁-C₈-alkyle, hydroxy-C₁-C₈-alkyle, hydroxyle, C₁-C₈-alcoxy, C₁-C₈-alcoxy-C₁-C₈-alkyle, amino, N-C₁-C₈-alkylamino, N,N-di-C₁-C₈-alkylamino, C₁-C₈-alkylcarbonyle, halogéno-C₁-C₈-alkylcarbonyle, hydroxy-C₁-C₈-alkylcarbonyle ou C₁-C₈-alcoxy-C₁-C₈-alkylcarbonyle ;

où « hétérocyclyle » est choisi parmi oxiranyle, aziridinyle, oxétanyle, thiétanyle, acétitinyle, pyrrolidinyle, tétrahydrofuranyle, tétrahydro-thiophényle, 2,3-dihydrofuranyle, 2,5-dihydrofuranyle, 2,3-dihydrothiophényle, 1-pyrrolinyle, 2-pyrrolinyle, 3-pyrrolinyle, tétrahydropyranyle, pipéridinyle, tétrahydrothiopyranyle, morpholinyle, thiomorpholinyle, pipérazinyle, azépanyle, thiépanyle ou oxépanyle ; chacun d'eux étant non substitué ou substitué par 1-5 substituants choisis indépendamment parmi oxo, halogène, C₁-C₈-alkyle, halogéno-C₁-C₈-alkyle, hydroxy-C₁-C₈-alkyle, hydroxyle, C₁-C₈-alcoxy, C₁-C₈-alcoxy-C₁-C₈-alkyle, amino, N-C₁-C₈-alkylamino, N,N-di-C₁-C₈-alkylamino, C₁-C₈-alkylcarbonyle, halogéno-C₁-C₈-alkylcarbonyle, hydroxy-C₁-C₈-alkylcarbonyle ou C₁-C₈-alcoxy-C₁-C₈-alkylcarbonyle ;

où « hétérocyclyle » peut être fixé au niveau d'un hétéroatome ou d'un atome de carbone et où les hétéroatomes de N et/ou S peuvent aussi être éventuellement oxydés jusqu'à divers états d'oxydation ;

où « hétéroaryle » est choisi parmi furanyle, thiophényle, pyrrolyle, imidazolyle, pyrazolyle, thiazolyle, isothiazolyle, oxazolyle, isoxazolyle, 1,2,5-oxadiazolyle, 1,2,4-oxadiazolyle, 1,2,3-oxadiazolyle, 1,3,4-oxadiazolyle, 1,2,5-thiadiazolyle, 1,2,4-thiadiazolyle, 1,2,3-thiadiazolyle, 1,3,4-thiadiazolyle, 1,2,3-triazolyle, 1,2,4-triazolyle, 1,2,5-triazolyle, pyridyle, pyrimidinyle, pyrazinyle, pyridazinyle, 1,2,3-triazinyle, 1,2,4-triazinyle

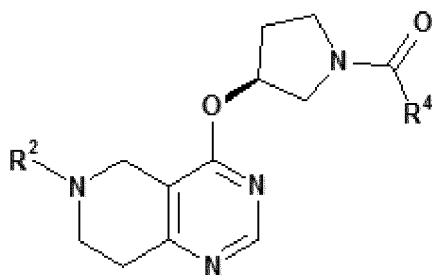
ou 1,3,5-triazinyle ; chacun d'entre eux étant non substitué ou substitué par 1-5 substituants choisis indépendamment parmi halogène, C₁-C₈-alkyle, halogéno-C₁-C₆-alkyle, hydroxy-C₁-C₈-alkyle, hydroxyle, C₁-C₈-alcoxy, C₁-C₈-alcoxy-C₁-C₈-alkyle, amino, N-C₁-C₈-alkylamino, N,N-di-C₁-C₈-alkylamino, C₁-C₈-alkylcarbonyl, halogéno-C₁-C₈-alkylcarbonyl, hydroxy-C₁-C₈-alkylcarbonyl ou C₁-C₈-alcoxy-C₁-C₈-alkylcarbonyl ; où « hétéroaryle » peut être fixé au niveau d'un hétéroatome ou d'un atome de carbone et où les hétéroatomes de N et/ou S peuvent aussi être éventuellement oxydés jusqu'à divers états d'oxydation ;

R² est choisi parmi phényle, naphtyle, pyridyle, pyrimidinyle, pyrazinyle, pyridazinyle, quinoléinyle ou isoquinoléinyle, chacun d'entre eux étant non substitué ou substitué par 1-5 substituants choisis indépendamment parmi halogène, cyano, nitro, C₁-C₈-alkyle, halogéno-C₁-C₈-alkyle, hydroxy-C₁-C₈-alkyle, hydroxyle, C₁-C₈-alcoxy, C₁-C₈-alcoxy-C₁-C₈-alkyle, amino, N-C₁-C₈-alkylamino, N,N-di-C₁-C₈-alkylamino, C₁-C₈-alkylcarbonyl, halogéno-C₁-C₈-alkylcarbonyl, hydroxy-C₁-C₈-alkylcarbonyl ou C₁-C₈-alcoxy-C₁-C₈-alkylcarbonyl ;

R³ est choisi parmi H, C₁-C₄-alkyle ou halogéno-C₁-C₄-alkyle ; et

m est choisi parmi 0 ou 1.

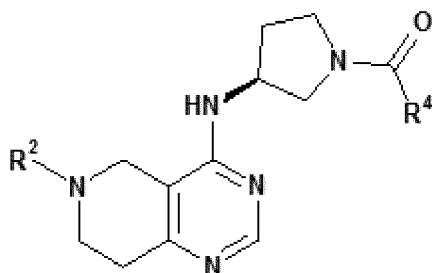
2. Inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, pour une utilisation selon la revendication 1, de formule (Id')



(Id'),

et/ou des tautomères et/ou N-oxydes et/ou sels pharmaceutiquement acceptables de celui-ci.

3. Inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, pour une utilisation selon la revendication 1, de formule (Ie')



(Ie'),

et/ou des tautomères et/ou N-oxydes et/ou sels pharmaceutiquement acceptables de celui-ci.

4. Inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, pour une utilisation selon l'une quelconque des revendications 1 à 3, dans lequel

R² est choisi parmi naphtyle, pyridyle ou pyrimidinyle ; chacun d'entre eux étant non substitué ou substitué par 1-3 substituants choisis indépendamment parmi halogène, cyano, nitro, C₁-C₈-alkyle, halogéno-C₁-C₈-alkyle, hydroxy-C₁-C₈-alkyle, hydroxyle, C₁-C₈-alcoxy, C₁-C₈-alcoxy-C₁-C₈-alkyle, amino, N-C₁-C₈-alkylamino, N,N-di-C₁-C₈-alkylamino, C₁-C₈-alkylcarbonyl, halogéno-C₁-C₈-alkylcarbonyl, hydroxy-C₁-C₈-alkylcarbonyl ou C₁-C₈-alcoxy-C₁-C₈-alkylcarbonyl.

5. Inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, pour une utilisation selon l'une quelconque des revendications 1 à 4, dans lequel

R¹, s'il est présent, est -C(O)-R⁴, où

R⁴ est choisi parmi hétérocyclyle, C₄-C₈-cycloalkyle ou hétéroaryle ;

où « C₃-C₁₂-cycloalkyle » peut être non substitué ou substitué par 1-3 substituants choisis indépendamment parmi fluoro, C₁-C₄-alkyle, hydroxyle, C₁-C₄-alcoxy ;

où « hétérocyclyle » est choisi parmi pyrrolidinyle, tétrahydropyranyle, pipéridinyle, tétrahydrothiopyranyle, morpholinyle ou pipérazinyle ; chacun d'entre eux étant non substitué ou substitué par 1-3 substituants choisis indépendamment parmi oxo, halogène, C₁-C₄-alkyle, hydroxyle, C₁-C₄-alkylcarbonyle ; où « hétérocyclyle » peut être fixé au niveau d'un hétéroatome ou d'un atome de carbone et où les hétéroatomes de N et/ou S peuvent aussi être éventuellement oxydés jusqu'à divers états d'oxydation ;

où « hétéroaryle » est choisi parmi furanyle, imidazolyle, pyrazolyle, thiazolyle, oxazolyle, isoxazolyle, 1,3,4-oxadiazolyle, pyridyle, pyrazinyle ; chacun d'entre eux étant non substitué ou substitué par 1-3 substituants choisis indépendamment parmi C₁-C₄-alkyle, hydroxyle ;

où « hétéroaryle » peut être fixé au niveau d'un hétéroatome ou d'un atome de carbone et où les hétéroatomes de N et/ou S peuvent aussi être éventuellement oxydés jusqu'à divers états d'oxydation.

6. Inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, pour une utilisation selon l'une quelconque des revendications 1 à 4, dans lequel

R¹, s'il est présent, est -C(O)-R⁴, et

R⁴ est choisi parmi C₁-C₈-alkyle, C₁-C₈-alcoxy-C₁-C₈-alkyle, C₁-C₈-alcoxy ou N,N-di-C₁-C₈-alkylamino,

où « C₁-C₈-alkyle » dans N,N-di-C₁-C₈-alkylamino peut être non substitué ou substitué par halogène, hydroxy ou C₁-C₄-alcoxy.

7. Inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, pour une utilisation selon la revendication 1, où l'inhibiteur de PI3K est choisi dans le groupe constitué par

la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tétrahydropyran-4-yl)méthanone ;

la {3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tétrahydropyran-4-yl)méthanone ;

la {(S)-3-[6-(2,4-diméthoxypyrimidin-5-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tétrahydropyran-4-yl)méthanone ;

la {3-[6-(2,4-diméthoxypyrimidin-5-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tétrahydropyran-4-yl)méthanone ;

le 2-méthoxy-5-{4-[(S)-1-(tétrahydropyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]-pyrimidin-6-yl}nicotinonitrile ;

le 2-méthoxy-5-{4-[1-(tétrahydropyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]-pyrimidin-6-yl}nicotinonitrile ;

la 1-{(S)-3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-propan-1-one ;

la 1-{3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-propan-1-one ;

la {(S)-3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tétrahydropyran-4-yl)méthanone ;

la {3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tétrahydropyran-4-yl)méthanone ;

le 2-amino-5-{4-[(S)-1-(tétrahydropyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]-pyrimidin-6-yl}nicotinonitrile ;

le 2-amino-5-{4-[1-(tétrahydropyran-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]-pyrimidin-6-yl}nicotinonitrile ;

la (S)-3-[6-(5-fluoro-6-méthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tétrahydro-2H-pyran-4-yl)méthanone ;

la {3-[6-(5-fluoro-6-méthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(tétrahydro-2H-pyran-4-yl)méthanone ;

le (S)-2-méthoxy-5-{4-[1-(2-méthoxyacétyl)pyrrolidin-3-yloxy]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl}-nicotinonitrile ;

le 2-méthoxy-5-{4-[1-(2-méthoxyacétyl)pyrrolidin-3-yloxy]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl}-nicotinonitrile ;

le (S)-5-{4-[1-(cyclopentanecarbonyl)pyrrolidin-3-yloxy]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl}-2-méthoxynicotinonitrile ;

le 5-(4-(1-(cyclopentanecarbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-méthoxy-nicotinonitrile ;

la (2,4-diméthyl-oxazol-5-yl)-{(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]-pyrimidin-4-yloxy]pyrrolidin-1-yl}méthanone ;

la (2,4-diméthyl-oxazol-5-yl)-{3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]-pyrimidin-4-yloxy]pyrrolidin-1-yl}méthanone ;

la furan-3-yl-{(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}méthanone ;

la furan-3-yl-{3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}méthanone ;

la furan-3-yl-{(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}méthanone ;

la furan-3-yl-{3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}méthanone ;

la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-méthyl-3H-imidazol-4-yl)méthanone ;

la {3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-méthyl-3H-imidazol-4-yl)méthanone ;

la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2-méthyl-oxazol-4-yl)méthanone ;

la {3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2-méthyl-oxazol-4-yl)méthanone ;

la (3-méthoxy-cyclobutyl)-{(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]-pyrimidin-4-yloxy]pyrrolidin-1-yl}méthanone ;

la (3-méthoxy-cyclobutyl)-{3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}méthanone ;

la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-4-yl-méthanone ;

la {(3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)oxazol-4-yl-méthanone ;

la 1-(4-((S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl)-pipéridin-1-yl)éthanone ;

la 1-(4-{3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidine-1-carbonyl}-pipéridin-1-yl)éthanone ;

la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(4-méthyl-oxazol-5-yl)méthanone ;

la {3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(4-méthyl-oxazol-5-yl)méthanone ;

la 5-((S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl)-1H-pyridin-2-one ;

la 5-{3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidine-1-carbonyl}-1H-pyridin-2-one ;

la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(1-méthyl-1H-imidazol-4-yl)méthanone ;

la {3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(1-méthyl-1H-imidazol-4-yl)méthanone ;

la {(S)-3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-4-yl-méthanone ;

la {3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-4-yl-méthanone ;

la {(S)-3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-5-yl-méthanone ;

la {3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}oxazol-5-yl-méthanone ;

la {(S)-3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2-méthyl-oxazol-4-yl)méthanone ;

la {3-[6-(5,6-diméthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2-méthyl-oxazol-4-yl)méthanone ;

la {(S)-3-[6-(5,6-diméthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2,2-diméthyl-tétrahydropyran-4-yl)méthanone ;
la {3-[6-(5,6-diméthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2,2-diméthyl-tétrahydropyran-4-yl)méthanone ;
5 la {(S)-3-[6-(5,6-diméthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2,4-diméthyl-oxazol-5-yl)méthanone ;
la {3-[6-(5,6-diméthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(2,4-diméthyl-oxazol-5-yl)méthanone ;
10 la (4,4-difluoro-cyclohexyl)-{(S)-3-[6-(5,6-diméthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}méthanone ;
la (4,4-difluoro-cyclohexyl)-{3-[6-(5,6-diméthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}méthanone ;
le 2-méthoxy-5-{4-[(S)-1-(2-tétrahydropyran-4-yl-acétyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinonitrile ;
15 le 2-méthoxy-5-{4-[1-(2-tétrahydropyran-4-yl-acétyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]-pyrimidin-6-yl}nicotinonitrile ;
le 5-{4-[(S)-1-(2,4-diméthyl-oxazole-5-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]-pyrimidin-6-yl}-2-méthoxy-nicotinonitrile ;
20 le 5-{4-[1-(2,4-diméthyl-oxazole-5-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-méthoxy-nicotinonitrile ;
le 5-{4-[(S)-1-(2,2-diméthyl-tétrahydropyran-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-méthoxy-nicotinonitrile ;
le 5-{4-[1-(2,2-diméthyl-tétrahydropyran-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-2-méthoxy-nicotinonitrile ;
25 la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(5-méthyl-oxazol-4-yl)méthanone ;
la {3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(5-méthyl-oxazol-4-yl)méthanone ;
30 la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(5-méthylisoxazol-4-yl)méthanone ;
la {3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(5-méthylisoxazol-4-yl)méthanone ;
la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-méthylisoxazol-4-yl)méthanone ;
35 la {3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-méthylisoxazol-4-yl)méthanone ;
la {(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-méthylisoxazol-4-yl)méthanone ;
40 la {3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}-(3-méthylisoxazol-4-yl)méthanone ;
l'isoxazol-3-yl-[(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}méthanone ;
l'isoxazol-3-yl-{3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}méthanone ;
45 l'isoxazol-5-yl-[(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}méthanone ;
l'isoxazol-5-yl-{3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}méthanone ;
50 le 2-méthoxy-5-{4-[(S)-1-(thiazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]-pyrimidin-6-yl}nicotinonitrile ;
le 2-méthoxy-5-{4-[1-(thiazole-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-nicotinonitrile ;
le 2-méthoxy-5-{4-[(S)-1-(1-méthyl-1H-pyrazole-4-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinonitrile ;
55 le 2-méthoxy-5-{4-[1-(1-méthyl-1H-pyrazole-4-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]-pyrimidin-6-yl}nicotinonitrile ;
le 2-méthoxy-5-{4-[(S)-1-(1-méthyl-1H-pyrazole-3-carbonyl)pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}nicotinonitrile ;

le 2-méthoxy-5-{4-[1-(1-méthyl-1H-pyrazole-3-carbonyl)-pyrrolidin-3-yloxy]-7,8-dihydro-5H-pyrido[4,3-d]-pyrimidin-6-yl}nicotinonitrile ;

la (2,2-diméthyl-tétrahydropyran-4-yl)-{(S)-3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}méthanone ;

la (2,2-diméthyl-tétrahydropyran-4-yl)-{3-[6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]-pyrimidin-4-yloxy]pyrrolidin-1-yl}méthanone ;

la (1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-{(S)-3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}méthanone ;

la (1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-{3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl}méthanone ;

la (S)-(2,4-diméthylloxazol-5-yl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-méthanone ;

la (2,4-diméthylloxazol-5-yl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-méthanone ;

la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(thiazol-5-yl)méthanone ;

la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(thiazol-5-yl)méthanone ;

la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(1-méthyl-1H-pyrazol-5-yl)méthanone ;

la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(1-méthyl-1H-pyrazol-5-yl)méthanone ;

la 4-((S)-3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carbonyl)pyrrolidin-2-one ;

la 4-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carbonyl)pyrrolidin-2-one ;

la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(pyridin-3-yl)méthanone ;

la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(pyridin-3-yl)méthanone ;

la (S)-(1H-imidazol-4-yl)(3-(6-(6-méthoxy-5-(trifluoro-méthyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]-pyrimidin-4-yloxy)pyrrolidin-1-yl)méthanone ;

la (1H-imidazol-4-yl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]-pyrimidin-4-yloxy)pyrrolidin-1-yl)méthanone ;

la 5-((S)-3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carbonyl)pyrrolidin-2-one ;

la 5-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carbonyl)pyrrolidin-2-one ;

la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(pyridin-4-yl)méthanone ;

la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(pyridin-4-yl)méthanone ;

la (S)-(1,3-diméthyl-1H-pyrazol-4-yl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-méthanone ;

la (1,3-diméthyl-1H-pyrazol-4-yl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-méthanone ;

la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(1H-pyrazol-4-yl)méthanone ;

la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(1H-pyrazol-4-yl)méthanone ;

la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(5-méthyl-1,3,4-oxadiazol-2-yl)-méthanone ;

la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(5-méthyl-1,3,4-oxadiazol-2-yl)-méthanone ;

la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(pyrazin-2-yl)méthanone ;

la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(pyrazin-2-yl)méthanone ;

- la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(1-méthyl-1H-imidazol-4-yl)méthanone ;
- la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(1-méthyl-1H-imidazol-4-yl)méthanone ;
- 5 la {(S)-3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(1-méthyl-1H-pyrazol-4-yl)méthanone ;
- la {3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(1-méthyl-1H-pyrazol-4-yl)méthanone ;
- 10 la {(S)-3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-thiazol-4-yl)méthanone ;
- la {3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-thiazol-4-yl)méthanone ;
- la {(S)-3-[6-(5-chloro-6-méthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tétrahydropyran-4-yl)méthanone ;
- 15 la {3-[6-(5-chloro-6-méthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tétrahydropyran-4-yl)méthanone ;
- la (S)-(3-(6-(6-amino-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;
- 20 la (3-(6-(6-amino-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;
- la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-azétidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;
- la {(S)-3-[6-(2-méthoxy-pyrimidin-5-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tétrahydro-pyran-4-yl)méthanone ;
- 25 la {3-[6-(2-méthoxy-pyrimidin-5-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tétrahydro-pyran-4-yl)méthanone ;
- la [(S)-3-(6-quinoléin-3-yl-5,6,7,8-tétrahydropyrido-[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-(tétrahydro-pyran-4-yl)méthanone ;
- 30 la [3-(6-quinoléin-3-yl-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)-(tétrahydro-pyran-4-yl)méthanone ;
- la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;
- la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;
- 35 la (S)-1-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)-3,3-diméthylbutan-1-one ;
- la 1-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)-3,3-diméthylbutan-1-one ;
- 40 la 1-((S)-3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)propan-1-one ;
- la 1-{3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}propan-1-one ;
- le 2-méthoxy-5-[4-((S)-1-propionyl-pyrrolidin-3-yloxy)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-nicotinonitrile ;
- le 2-méthoxy-5-[4-(1-propionyl-pyrrolidin-3-yloxy)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-nicotinonitrile ;
- 45 la (S)-6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-4-(1-(pyridin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidine ;
- la 6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-4-(1-(pyridin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidine ;
- 50 la (S)-6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-4-(1-(pyrimidin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidine ;
- la 6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-4-(1-(pyrimidin-2-yl)pyrrolidin-3-yloxy)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidine ;
- la (S)-1-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yl-amino)pyrrolidin-1-yl)propan-1-one ;
- 55 la 1-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yl-amino)-pyrrolidin-1-yl)propan-1-one ;
- la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yl-amino)pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)-méthanone ;

la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;
 le (S)-2-méthoxy-5-(4-(1-(tétrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-ylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile ;
 5 le 2-méthoxy-5-(4-(1-(tétrahydro-2H-pyran-4-carbonyl)-pyrrolidin-3-ylamino)-7,8-dihydropyrido[4,3-d]-pyrimidin-6(5H)-yl)nicotinonitrile ;
 la (S)-1-(4-(3-(6-(6-méthoxy-5-(trifluorométhyl)-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidine-1-carbonyl)pipéridin-1-yl)-éthanone ;
 la 1-(4-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yl-amino)pyrrolidine-1-carbonyl)pipéridin-1-yl)éthanone ;
 10 la (2,2-diméthyltétrahydro-2H-pyran-4-yl)((S)-3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)méthanone ;
 la (2,2-diméthyltétrahydro-2H-pyran-4-yl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)méthanone ;
 15 la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yl-amino)pyrrolidin-1-yl)(oxazol-5-yl)méthanone ;
 la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidin-1-yl)(oxazol-5-yl)méthanone ;
 la ((S)-3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yl-amino)pyrrolidin-1-yl)((1s,4R)-4-méthoxycyclohexyl)-méthanone ;
 20 la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidin-1-yl)((1s,4R)-4-méthoxycyclohexyl)-méthanone ;
 la ((S)-3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yl-amino)pyrrolidin-1-yl)((1r,4S)-4-méthoxycyclohexyl)-méthanone ;
 25 la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidin-1-yl)((1r,4S)-4-méthoxycyclohexyl)-méthanone ;
 la ((1s,4R)-4-hydroxycyclohexyl)((S)-3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)-méthanone ;
 la ((1s,4R)-4-hydroxycyclohexyl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)-méthanone ;
 30 la ((1r,4S)-4-hydroxycyclohexyl)((S)-3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)-méthanone ;
 la ((1r,4S)-4-hydroxycyclohexyl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)-méthanone ;
 35 la (S)-(3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(1-méthyl-1H-imidazol-4-yl)méthanone ;
 la (3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(1-méthyl-1H-imidazol-4-yl)méthanone ;
 la (S)-(3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)méthanone ;
 40 la (3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-5-yl)méthanone ;
 la (S)-(3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-4-yl)méthanone ;
 45 la (3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(oxazol-4-yl)méthanone ;
 la (2,2-diméthyltétrahydro-2H-pyran-4-yl)((S)-3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)méthanone ;
 la (2,2-diméthyltétrahydro-2H-pyran-4-yl) (3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)méthanone ;
 50 la (S)-1-(3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidin-1-yl)propan-1-one ;
 la 1-(3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)propan-1-one ;
 55 la (S)-(3-(6-(5-chloro-6-méthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;
 la (3-(6-(5-chloro-6-méthoxypyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;

la (S)-(3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;
la (3-(6-(6-méthoxy-5-méthylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)(tétrahydro-2H-pyran-4-yl)méthanone ;
5 la (tétrahydropyran-4-yl)-{(S)-3-[6-(5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]-pyrimidin-4-ylamino)pyrrolidin-1-yl}méthanone ;
la (tétrahydropyran-4-yl)-{3-[6-(5-(trifluorométhyl)-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-ylamino)pyrrolidin-1-yl}méthanone ;
la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(4-méthylpipérazin-1-yl)méthanone ;
10 la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(4-méthylpipérazin-1-yl)méthanone ;
la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(morpholino)méthanone ;
15 la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(morpholino)méthanone ;
la (S)-(4-hydroxypipéridin-1-yl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)méthanone ;
la 4-hydroxypipéridin-1-yl)(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidin-1-yl)méthanone ;
20 le (S)-N-(2-hydroxyéthyl)-3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]-pyrimidin-4-yloxy)-N-méthylpyrrolidine-1-carboxamide ;
le N-(2-hydroxyéthyl)-3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]-pyrimidin-4-yloxy)-N-méthylpyrrolidine-1-carboxamide ;
25 la (S)-1-(4-(3-(6-(6-méthoxy-5-(trifluorométhyl)-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)pyrrolidine-1-carbonyl)pipérazin-1-yl)-éthanone ;
la 1-(4-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carbonyl)pipérazin-1-yl)éthanone ;
le (S)-2-méthoxy-5-(4-(1-(morpholine-4-carbonyl)-pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)nicotinonitrile ;
30 le 2-méthoxy-5-(4-(1-(morpholine-4-carbonyl)pyrrolidin-3-yloxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-nicotinonitrile ;
la (S)-(3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(oxazol-4-yl)méthanone ;
35 la (3-(6-(6-méthoxy-5-(trifluorométhyl)pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidin-1-yl)(oxazol-4-yl)méthanone ;
la 1-(4-((S)-3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yl-oxy]pyrrolidine-1-carbonyl)-pipéridin-1-yl)éthanone ;
la 1-(4-{3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carbonyl}-pipéridin-1-yl)éthanone ;
40 la {(S)-3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(3-méthyl-3H-imidazol-4-yl)méthanone ;
la {3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl)-(3-méthyl-3H-imidazol-4-yl)méthanone ;
45 la {(S)-3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}oxazol-5-yl-méthanone ;
la {3-[6-(6-méthoxy-5-trifluorométhylpyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}oxazol-5-yl-méthanone ;
la {(S)-3-[6-(6-méthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tétrahydropyran-4-yl)méthanone ; et
50 la {3-[6-(6-méthoxy-pyridin-3-yl)-5,6,7,8-tétrahydropyrido[4,3-d]pyrimidin-4-yloxy]pyrrolidin-1-yl)-(tétrahydropyran-4-yl)méthanone.

8. Inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, pour une utilisation selon l'une quelconque des revendications 1 à 7 sous la forme d'un sel choisi parmi

- a) un citrate, fumarate ou napadisylate ; ou
b) un phosphate, chlorhydrate ou hippurate.

9. Composition pharmaceutique comprenant un inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, ou des sels ou solvates pharmaceutiquement acceptables de celui-ci, dans laquelle l'inhibiteur de PI3K est tel que défini selon l'une quelconque des revendications 1 à 8, pour une utilisation dans le traitement d'une immunopathologie chez un sujet souffrant d'une maladie ou d'un trouble choisi (e) parmi le paludisme aigu et cérébral, via l'inhibition fonctionnelle de TLR9 du sujet infecté.
10. Combinaison comprenant un inhibiteur de PI3K, où ledit inhibiteur possède une action inhibitrice sur l'isoforme delta de PI3K, ou des sels ou solvates pharmaceutiquement acceptables de celui-ci, dans laquelle l'inhibiteur de PI3K est tel que défini selon l'une quelconque des revendications 1 à 8, pour une utilisation dans le traitement d'une immunopathologie chez un sujet souffrant d'une maladie ou d'un trouble choisi(e) parmi le paludisme aigu et cérébral, via l'inhibition fonctionnelle de TLR9 du sujet infecté, et un ou plusieurs ingrédients actifs supplémentaires.

Figure 1

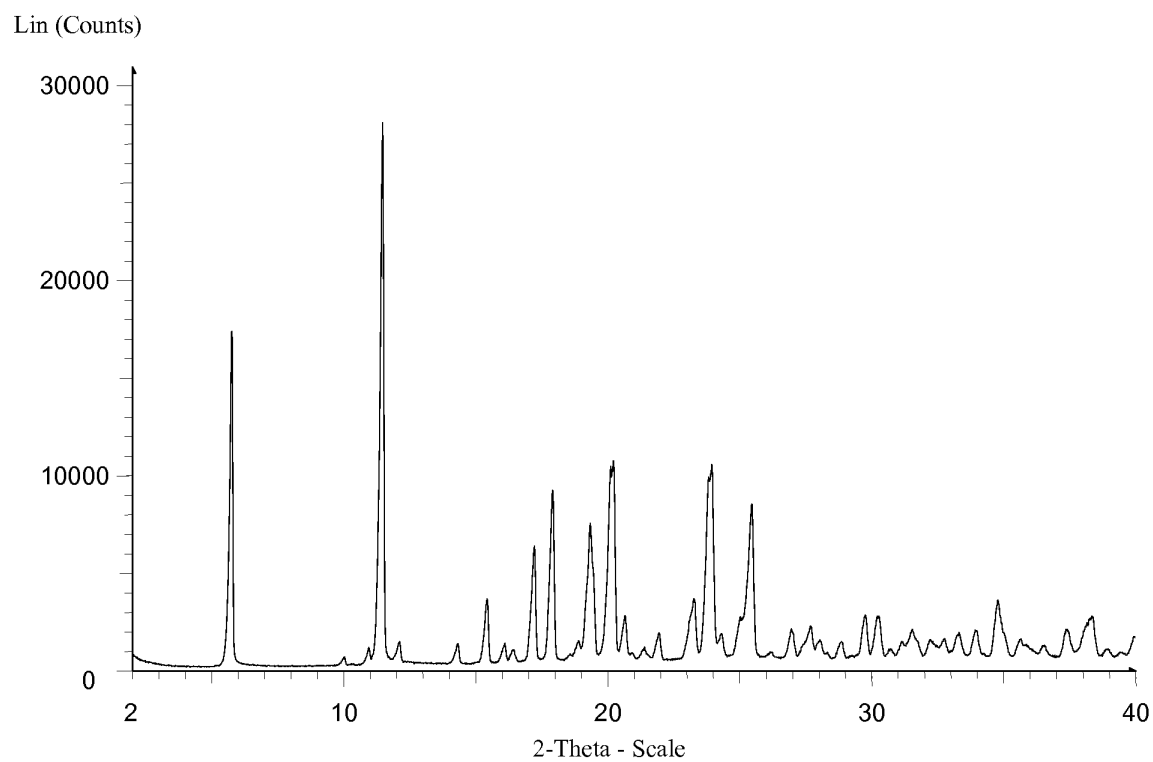


Figure 2

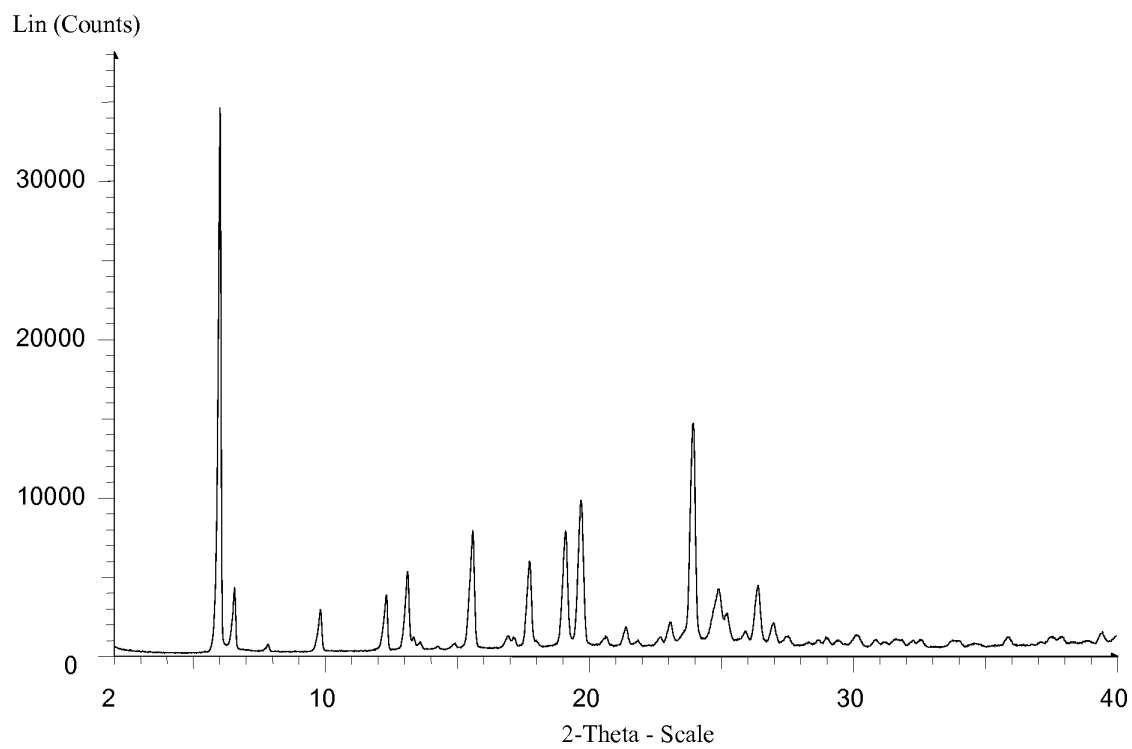


Figure 3

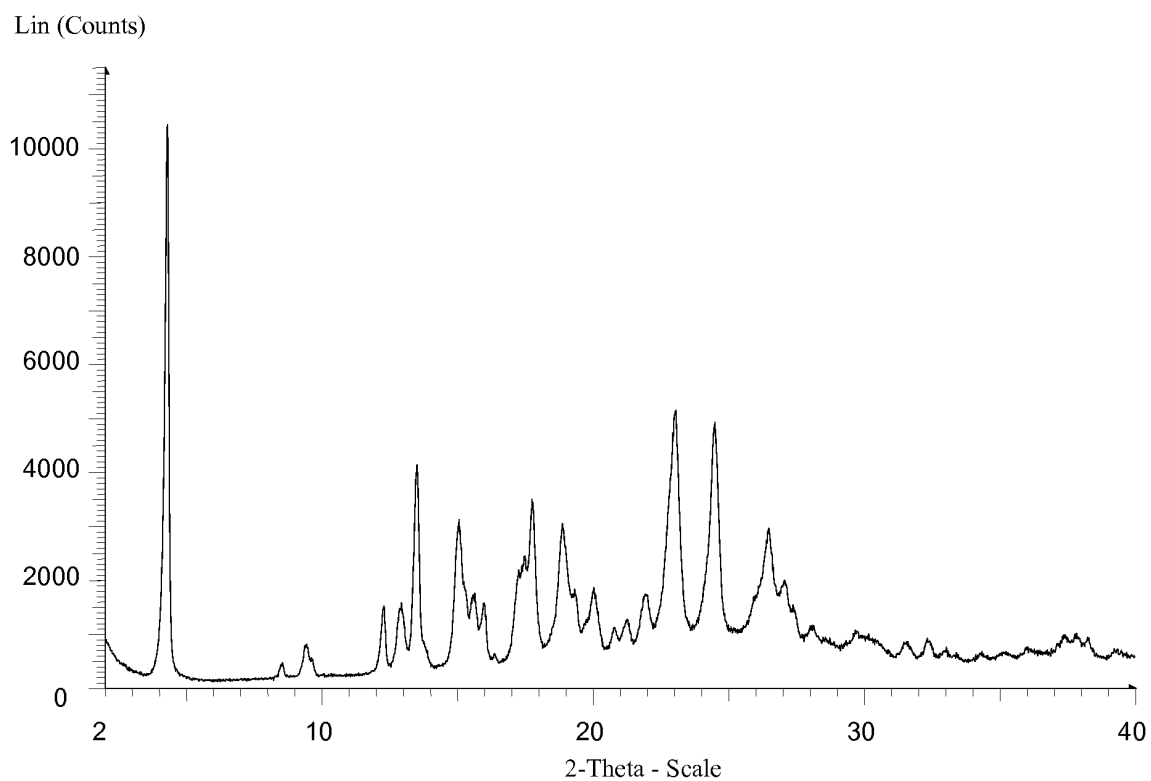


Figure 4

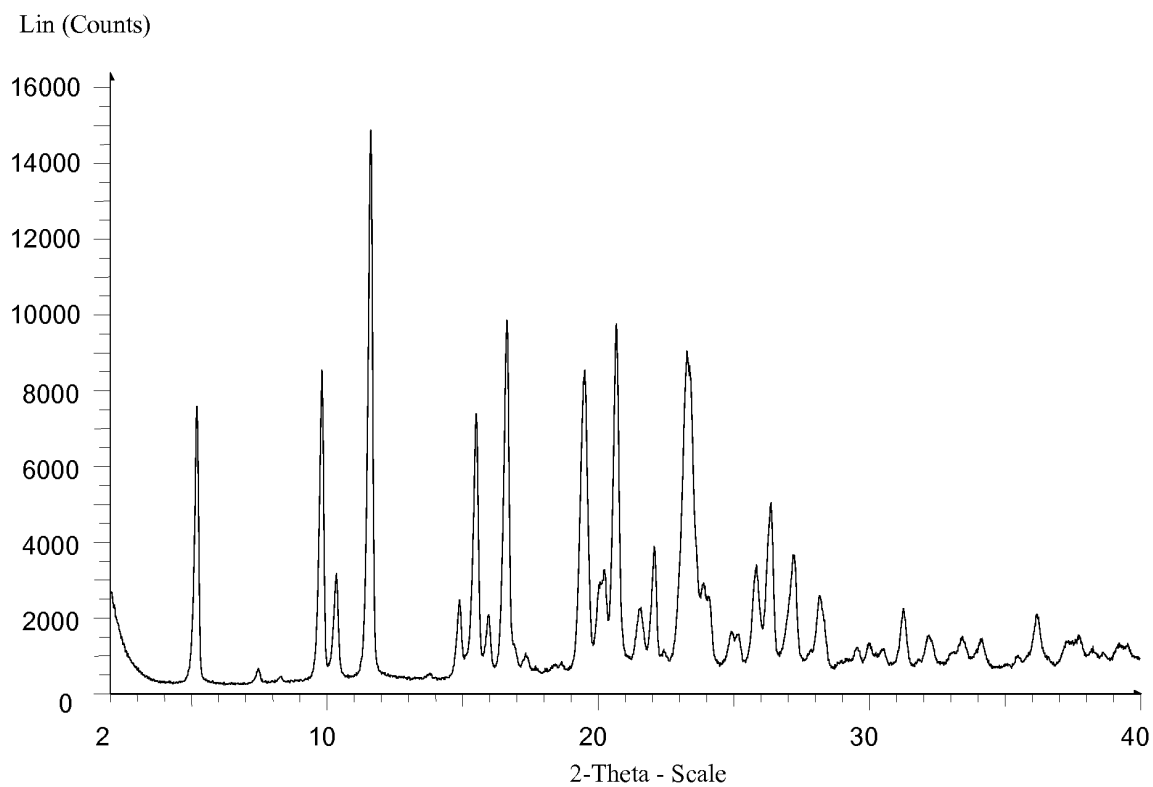


Figure 5

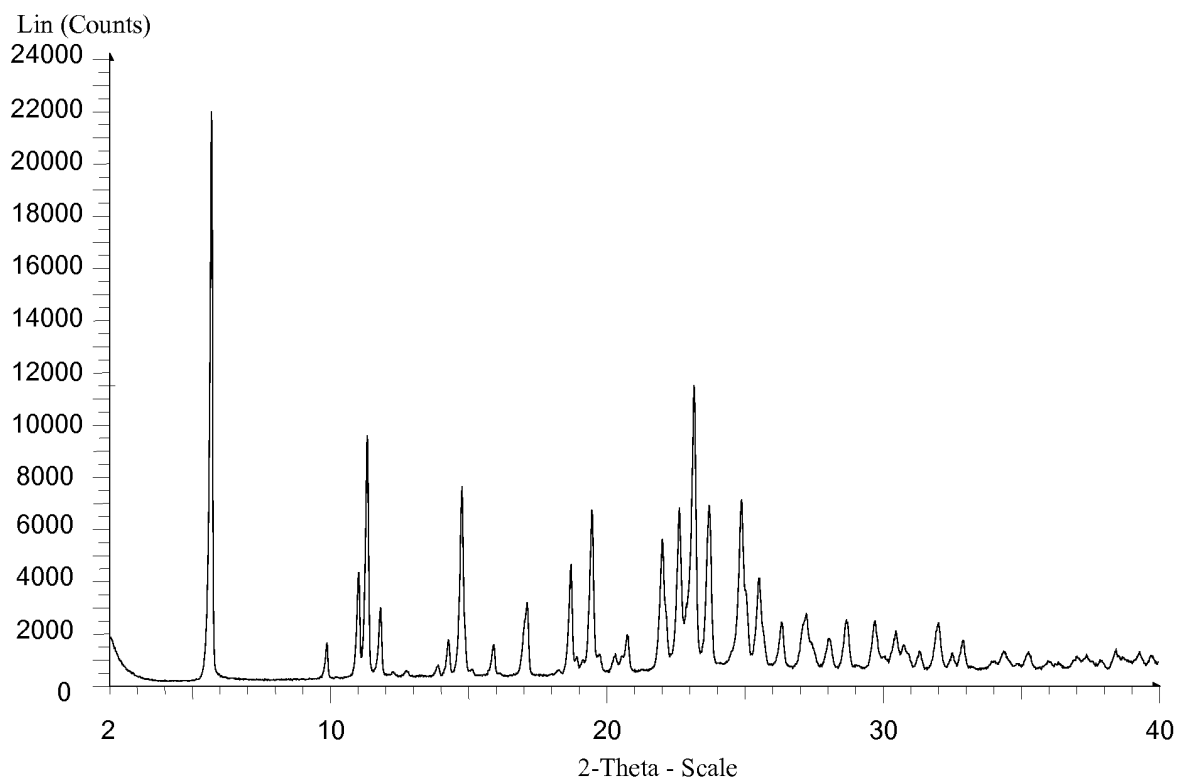


Figure 6

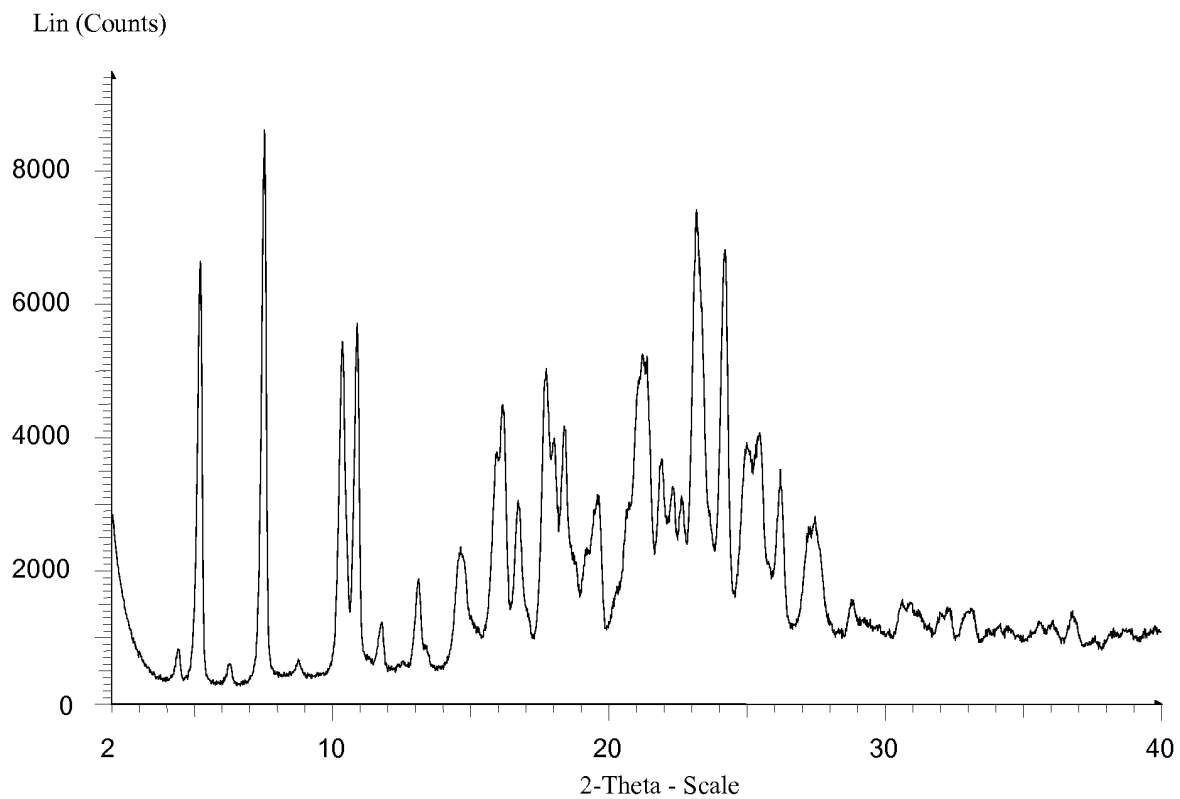


Figure 7

Lin (Counts)

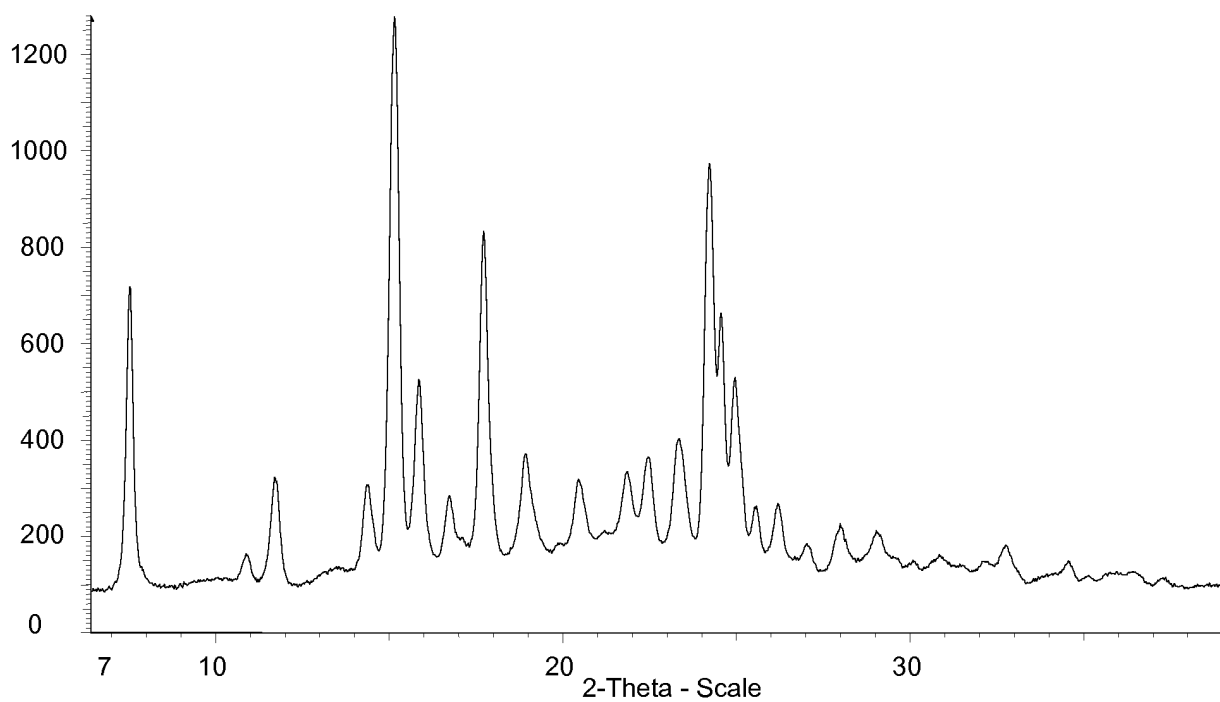


Figure 8

Lin (Counts)

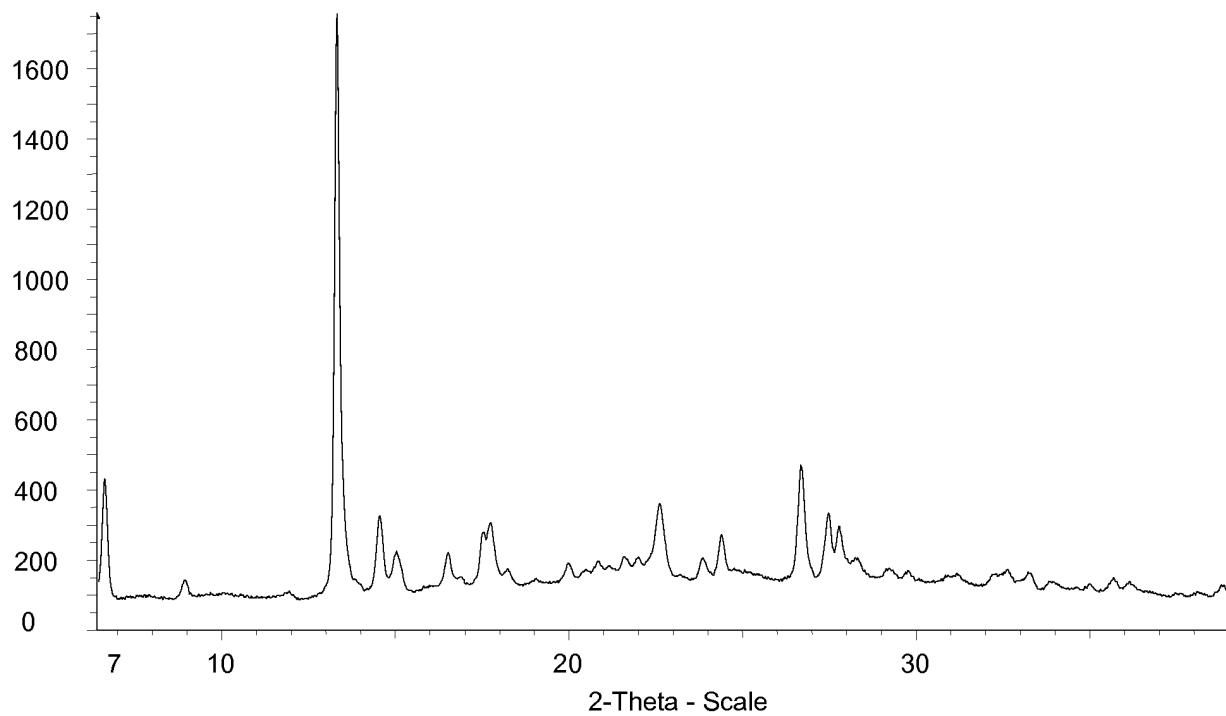
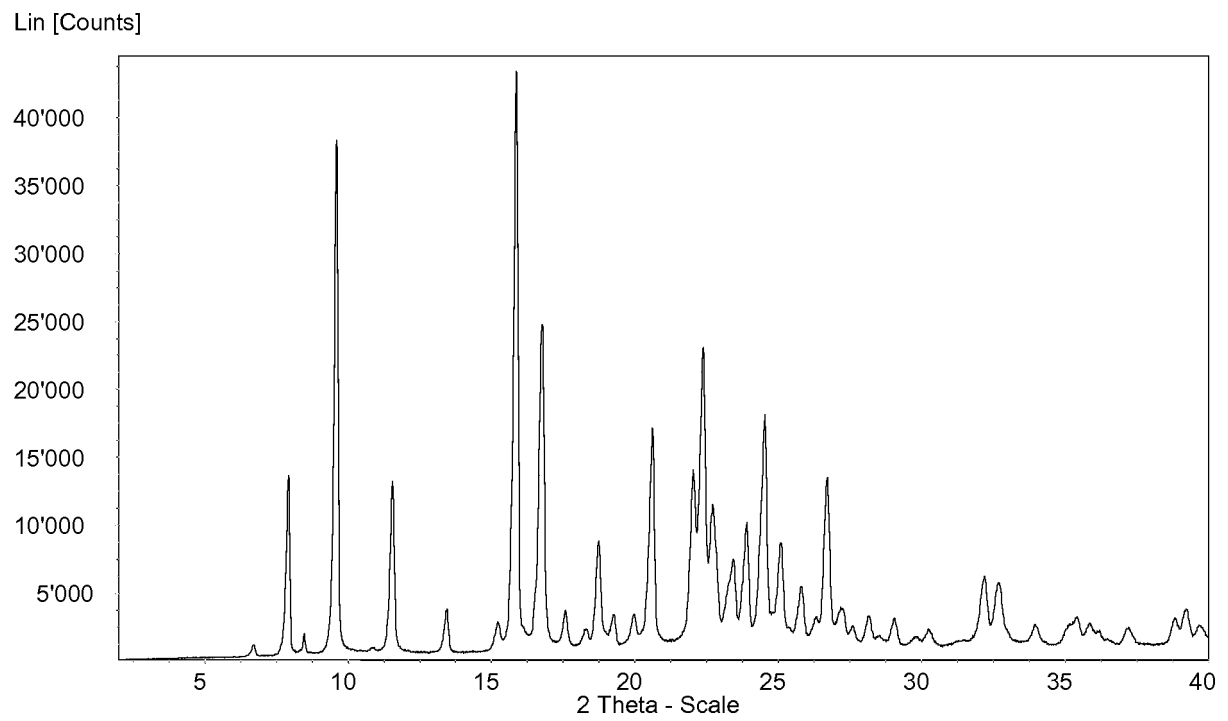


Figure 9



REFERENCES CITED IN THE DESCRIPTION

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